201-16113

Karen Hoffman/DC/USEPA/US
12/22/2005 09:53 AM

To NCIC HPV@EPA, JanetR Pope/DC/USEPA/US@EPA
cc Jeffrey Taylor/DC/USEPA/US@EPA
bcc
Subject Fw: HPV SUBMISSION for chlorinated pyridine category

Janet: this came into the Chemrtk inbox but did not have a cc to NCIC so I'm forwarding it to you for processing.

Thanks.

Karen Hoffman
----- Forwarded by Karen Hoffman/DC/USEPA/US on 12/22/2005 09:52 AM -----

"Hartwell, Gail" <ggarvin@dow.com>
12/21/2005 03:51 PM

To 'chem.rtk@epa.gov'
cc "Madsen, Steve (SS)" <ssmadsen@dow.com>, "Eisenbrandt, Dave" <dleisenbrandt@dow.com>, "Kranzfelder, James (JA)" <JKranzfelder@dow.com>, "Burgert, Linda (LC)" <lburgert@dow.com>, "Clark, Martin (JT)" <JTCLARK@dow.com>, "Berdasco, Nancy (NM)" <NMBerdasco@dow.com>
Subject HPV SUBMISSION for chlorinated pyridine category

05 DEC 27 AM 9:47
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> Sir: Dow AgroSciences has enclosed the HPV documents for chlorinated pyridine category, which includes 2,3,4,5,6-pentachloropyridine (CAS No. 2176-62-7), 3,4,5,6-tetrachloro-2-pyridine carbonitrile (CAS No. 17824-83-8), 3,6-dichloro-2-trichloromethylpyridine (CAS No. 1817-13-6), 2-chloro-5-trichloromethylpyridine (CAS No. 69045-78-9), chloropyridine derivatives (CAS No. 68412-40-8), methyl chloropyridine derivatives (CAS No. 70024-85-0) and for purposes of enriching the database for this category, 2,3,5,6-tetrachloropyridine (CAS No. 2402-79-1). Justification for categorization is discussed in the test plan and existing data are summarized. No additional data are needed under the HPV Challenge Program. We wish to have all documents posted on the EPA website for HPV chemicals. I have enclosed a cover letter, and a robust summary for each molecule included in this category. Please do not hesitate to contact me if you have any questions or comments.
>
> > <<Chlorinated Pyridine Category Test Plan.pdf>> > > <<2-Chloro-5-trichloromethylpyridine CAS 69045-78-9.pdf>> > > <<3,6-Dichloro-2-trichloromethylpyridine CAS 1817-13-6.pdf>> > > <<Chloropyridine derivatives CAS 68412-40-8.pdf>> > > <<Methyl chloropyridine derivatives CAS 70024-85-0.pdf>> > > <<Pentachloropyridine CAS 2176-62-7.pdf>> > > <<2,3,5,6-Tetrachloropyridine _Symtet_ CAS 2402-79-1 .pdf>> > > <<3,4,5,6-Tetrachloro-2-pyridine carbonitrile CAS 17824-83-8..pdf>>
> Thanks,

Gail M. Hartwell
Dow AgroSciences LLC
EH&S Improvement Specialist
9330 Zionsville Road
Indianapolis, IN 46268
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ggarvin@dow.com

Chlorinated Pyridine Category Test Plan.pdf 2-Chloro-5-trichloromethylpyridine CAS 69045-78-9.pdf

3,6-Dichloro-2-trichloromethylpyridine CAS 1817-13-6.pdf Chloropyridine derivatives CAS 68412-40-8.pdf

Methyl chloropyridine derivatives CAS 70024-85-0.pdf Pentachloropyridine CAS 2176-62-7.pdf

2,3,5,6-Tetrachloropyridine _Symtet_ CAS 2402-79-1 .pdf 3,4,5,6-Tetrachloro-2-pyridine carbonitrile CAS 17824-83-8..pdf

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HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For

CHLORINATED PYRIDINE CATEGORY

Prepared by:

The Dow Chemical Company

December 15, 2005

TABLE OF CONTENTS
TEST PLAN FOR CHLORINATED PYRIDINE CATEGORY

PLAIN ENGLISH SUMMARY

This test plan addresses the chemical category of chlorinated pyridines, which includes 2,3,4,5,6-pentachloropyridine (CAS No. 2176-62-7), 3,4,5,6-tetrachloro-2-pyridine carbonitrile (CAS No. 17824-83-8), 3,6-dichloro-2-trichloromethylpyridine (CAS No. 1817-13-6), 2-chloro-5-trichloromethylpyridine (CAS No. 69045-78-9), chloropyridine derivatives (CAS No. 68412-40-8), and methyl chloropyridine derivatives (CAS No. 70024-85-0). In addition, for purposes of enriching the database for this category, 2,3,5,6-tetrachloropyridine (CAS No. 2402-79-1) has been included. Existing data are summarized. No additional data are needed under the HPV Challenge Program.

EXECUTIVE SUMMARY

The Dow Chemical Company hereby submits for review and public comment the test plan for the chlorinated pyridine category under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of The Dow Chemical Company to use a variety of existing data and scientific judgment/analyses to adequately characterize the SIDS (Screening Information Data Set) human health, environmental fate and effects, and physicochemical endpoints for this chemical stream.

Chemical Category: Chlorinated Pyridines

1. *Identification of category and Rationale for Use*

The Chlorinated Pyridines category is defined as a structurally related group of chlorinated pyridine molecules, and includes several process streams of related process byproducts. All of these chemicals have a common Structure-Activity-Relationship (SAR) to serve as the technical basis for the category under the EPA HPV Challenge Program.

In the EPA Guidance Document entitled Development of Chemical Categories in the HPV Challenge Program, under Section II entitled Definitions, the following information is given:
"A chemical category, for the purposes of the Challenge Program, is a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. These structural similarities may create a predictable pattern in any or all of the following parameters: physicochemical properties, environmental fate and environmental effects, and human health effects. The similarities may be based on the following:

- a common functional group[e.g., aldehyde, epoxide, ester, etc.]; or
- the likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally similar chemicals [e.g., the "family approach" of examining related chemicals such as acid/ester/salt]; and
- an incremental and constant change across the category [e.g., the dimethylene group difference between adjacent members of the alpha-olefins]-"

The Chlorinated Pyridine Category proposed herein complies with the EPA definition of an acceptable Category based on all three criteria cited above, namely

[a] the sharing of a common functional group (all chlorinated derivative of a pyridine backbone),
[b] the likelihood of common precursors and/or breakdown products via physical or biological processes, which result in structurally similar chemicals, and
[c] incremental changes in chemical structure as one progresses from lower to higher states of chlorination of the pyridine backbone.

All category members (except 2,3,4,5,6-pentachloropyridine, which qualifies as a production chemical) should be regarded as site-limited intermediates, based on the extremely limited potential for exposure during manufacturing, transport, consumption and use.

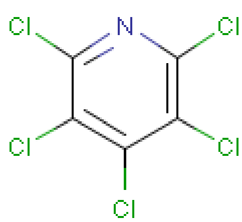
These chemicals/process streams are used in other site manufacturing processes or are converted to feedstock for chlorine production, with no sales or off-site transport, and thus little potential for exposure of non-employee populations.

Although the chemicals are isolated during manufacture, the potential for employee exposure is similarly low, usually only during maintenance or site-limited transport procedures (see the specific chemical for more detail).

The group consists of molecules with a pyridinyl backbone, with varying levels of chlorination; some have other chemical moieties in addition to the chlorine atoms (e.g., methyl groups); two of the category members are process streams of mixed chlorinated pyridines.

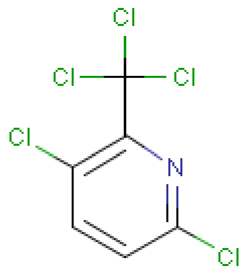
The chemicals included in this category are:

A. 2,3,4,5,6-Pentachloropyridine
CAS # 2176-62-7



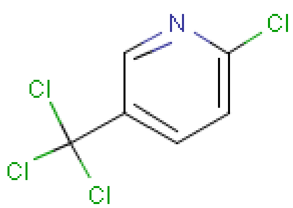
This material is a production chemical, under the conditions of the US EPA HPV Challenge Program.

B.	3,6-Dichloro-2-trichloromethylpyridine
CAS # 1817-13-6



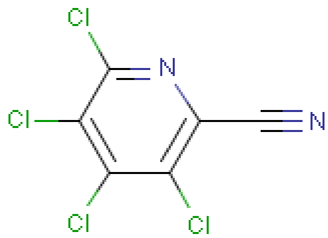
Potential for employee exposure to this material is low: the material is totally contained via hard piping and pumped to a reactor for pesticide production; lines are opened periodically for sampling, or for maintenance as required; recommended personal protective equipment comprises full chemical protective clothing, including gloves, boots, chemical suiting, eye protection, and respirators, and all necessary precautions are taken to avoid spills and leaks during sampling and maintenance.

C.	2-Chloro-5-trichloromethylpyridine
CAS # 69045-78-9



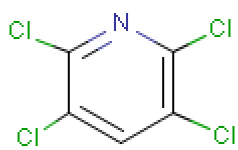
Potential for employee exposure to this material is low: the material is totally contained via hard piping and pumped to a reactor for pesticide production; lines are opened periodically for sampling, or for maintenance as required; recommended personal protective equipment comprises full chemical protective clothing, including gloves, boots, chemical suiting, eye protection, and respirators, and all necessary precautions are taken to avoid spills and leaks during sampling and maintenance.

D.	3,4,5,6-Tetrachloro-2-pyridine carbonitrile
CAS # 17824-83-8



Potential for employee exposure to this material is low: the material is totally contained via hard piping and pumped to a reactor for pesticide production; lines are opened periodically for sampling, or for maintenance as required; recommended personal protective equipment comprises full chemical protective clothing, including gloves, boots, chemical suiting, eye protection, and respirators, and all necessary precautions are taken to avoid spills and leaks during sampling and maintenance.

E. 2,3,5,6-Tetrachloropyridine
CAS # 2402-79-1



Potential for employee exposure to this material is low: the material is totally contained via hard piping and pumped to a reactor for pesticide production; lines are opened periodically for sampling, or for maintenance as required; recommended personal protective equipment comprises full chemical protective clothing, including gloves, boots, chemical suiting, eye protection, and respirators, and all necessary precautions are taken to avoid spills and leaks during sampling and maintenance.

F. Chloropyridine derivatives
CAS # 68412-40-8
No structure is included for this chemical mixture, since it is a process stream composed of the following components:

Pentachloropyridine	3.3%
2,3,4,6-Tetrachloro-5-pyridinecarbonitrile	0.1%

Hexachlorobenzene	16.2%
Pentachloroethynylpyridine	28.1%
3,4,5,6-Tetrachloro-1,2-benzenedicarbonitrile	0.8%
2,4,5,6-Tetrachloro-1,3-benzenedicarbonitrile	1.4%
Trichloroethylenetetrachloropyridine isomers (3 isomers)	9.5%
Pentachloro(trichloroethenyl)-benzene	1.0%
1,2,4-Trichloro-5-[(chloropheny)thio]benzene	0.2%
Tetrachlorodihydromethylbenzo(A)carbazole isomers (3 isomers)	0.9%
Hexachlorobipyridylene Isomers/Derivatives (3 isomers/derivatives)	0.5%
Perchlorovinylcyanopyridine isomers (2 isomers)	0.7%
4-[p-bis(2-hydroxyethylamino]phenyl-1-bromoisoquinoline	2.0%
Heptachlorobipyridylene Isomers/Derivatives (2 isomers/derivatives)	1.1%
Octachlorobipyridylene Isomers/Derivatives (5 isomers/derivatives)	6.7%
Trichlorovinyltetrachloroethynylpyridine	9.8%
Hexachlorobipyridylene Isomers/Derivatives (9 isomers/derivatives)	16.5%
Nonachlorophenylpyridine	0.2%
Octachloronaphthalene	0.7%
Heptachlorobipyridylene Isomer or Derivative	0.3%
Irieol	0.4%

It should be noted that the percentages indicated above represent data gathered at one point in time, and vary with the time the process stream was sampled.

Potential for employee exposure to this material is low: the material is transferred to a tank car for transport to a reactor on site 3-4 times per week; recommended personal protective equipment comprises full chemical protective clothing, including gloves, boots, chemical suiting, eye protection, and respirators, and all necessary precautions are taken to avoid spills and leaks during sampling and maintenance.

G. Methyl chloropyridine derivatives
CAS # 70024-85-0

No structure is included for this chemical mixture, since it is a process stream composed of the following components:

1,2,3,4,11-Pentachloro-8-(trichloromethyl) dipyrioimidazolium tetrachloroferrate and process contaminants	46%
Chlorinated pyridines	31%
Ferric chloride	15%
Chlorinated bipyridines	6%
Chlorohydrocarbons	2%

It should be noted that the percentages indicated above represent data gathered at one point in time, and vary with the time the process stream was sampled.

Potential for employee exposure to this material is low: the material is totally contained via hard piping and pumped to a reactor for burning/HCl reclamation; lines are opened every two weeks for sampling, or for maintenance as required; recommended personal protective equipment comprises full chemical protective clothing, including gloves, boots, chemical suiting, and full-face respirators, and all necessary precautions are taken to avoid spills and leaks during sampling and maintenance. Protective equipment is upgraded to include thermally protective gear when the material could be present at temperatures above 100º C.

2. Availability of Data for Members of Chemical Category and Analysis of Adequacy

Robust summaries of data available for all members of the category have been prepared, and are included in Appendix 1.

Table 1 documents the availability of SIDS endpoints and available/adequate data for members of the category. A complete dataset exists for the first member of the category, pentachloropyridine (2176-62-7), and for the fifth member of the category, tetrachloropyridine (2402-79-1). Physicochemical data for the remaining three single chemical category members were calculated where possible. Measured ecotoxicity data were available for one of the remaining single chemical category members (69045-78-9); data were calculated for another (17824-83-8). Measured data for acute mammalian toxicity endpoints were available for the three remaining single chemicals (1817-13-6, 69045-78-9, 17824-83-8). No measured data exist for the two category members which are process streams (68412-40-8, 70024-85-0), nor was calculation of data possible. However, the five single chemical category members are among the major components of the process streams, and some estimate of toxicity can be inferred from the single chemical category member data.

Table 1. Matrix of Available and Adequate Data on Chlorinated Pyridine Category Members							
Test	A. 2176-62-7	B. 1817-13-6	C.69045-78-9	D.17824-83-8	E. 2402-79-1	E. 68412-40-8	F. 70024-85-0
Physicochemical Properties							
Partition Coefficient	+	+[3]	[3]	[3]	+	-	-
Water Solubility	+	+[3]	[3]	[3]	+	-	-
Environmental Fate	+	+[3]	[3]	[3]	+	-	-
Biodegradation	+	+[3]	[3]	[3]	+	-	-
Environmental Transport	+	+[3]	[3]	[3]	[3]	-	-
Ecotoxicity							
Acute Fish	+	-	+	+[3]	+	-	-
Acute Daphnid	+[1]	-	+	+[3]	+	-	-
Alga	+	-	-	+[3]	+	-	-
Human Health Effects							
Acute	+	+	+	+	+	-	-
Repeated Dose	+	-[4]	[4]	-	+	-	-
Genotoxicity (*in vitro* – bacteria)	+	-	-	-	+	-	-
Genotoxicity (*in vitro* – non-bacterial)	+	-	-	-	-	-	-
Genotoxicity (*in vivo*)	+[2]	- -	-	-	+	-	-
Repro/Developmental	+	-	-	-	+	-	-

+ = Data available and considered adequate; - = No data available or considered inadequate

[1]Although there are no data for daphnids, three other species of invertebrates were tested.

[2]USEPA guidance indicates that a combination of *in vitro* tests (e.g., bacterial plus rat lymphocyte chromosomal aberration) serve to satisfy the requirement for an *in vivo* test.

[3]Calculated values.

[4]Two two-week studies were summarized and deemed adequate with restrictions; however, no longer-term studies were located.

3. *Comparison of Available Data for Category Members*

Review of the data currently available on these compounds confirms the validity of this category, with similar/predictable activity in regard to physical/chemical properties, environmental fate, environmental effects and human health effects to be addressed in the EPA HPV Testing program. All data are summarized in IUCLID dossiers for individual category members, included as appendices to this document.

Data for category members were evaluated for patterns between endpoints. Table 2 documents values for physicochemical properties among category members. Calculated values are indicated as such.

Table 2. Comparison of Physicochemical Data for Category Members

Category Member	Partition Coefficient (log POW)	Water Solubility (mg/L @ 25ºC)	Vapor Pressure (mm Hg @ 25ºC)	Melting Point (ºC)	Environmental Fate (photolysis rate constant in cm^3/mol*sec)	Environ-mental Transport (% in air, water, soil, sediment)
A. 2176-62-7	3.53	8.5	0.014	125-126	1.1E-14[1]	73.55, 6.5, 19.5, 0.43[1]
B. 1817-13-6	4[1]	7.5[1]	0.0052[1]	47-48	1.39E-14[1]	32.9, 6.7, 59.1, 1.3[1]
C.69045-78-9	3.35[1]	99	0.0105[1]	52-54	4.77E-14[1]	17.9, 27.1, 53.8, 1.2[1]
D.17824-83-8	2.93	45[1]	3.30E-5[1]	150.5-151.5	2.8E-12[1]	1.5, 55.6, 41.9, 0.9[1]
E. 2402-79-1	3.32	22.6	0.2002	90.5	1.53E-14	18.9, 28.0, 51.9, 1.2[1]
F. 68412-40-8	ND	ND	ND	ND	ND	ND
G. 70024-85-0	ND	ND	ND	ND	ND	ND

ND = No Data
[1]Calculated value.

For the single chemical category members, partition coefficients are similar and range from about 3 to a maximum of 4, indicating a moderate potential for bioconcentration, as might be expected based on water solubility.

The single chemical water solubility values encompass a range from 7.5 to 99 mg/L, although solubility does not seem to be correlated either to partitioning within the aquatic environment or to toxicity (see discussion of aquatic toxicity studies). With the relatively low water solubilities noted, and given the fact that the materials in question do not ionize at environmentally relevant pH, hydrolysis is not expected to be a significant factor in degradation.

All the single chemicals are low in vapor pressure, either estimated or measured values. Thus, as expected, the photolysis rate constants are very low for all single chemicals. There seems to be no basis for significant amounts of photodegradation for the category chemicals.

Fugacity values are similar for the chemicals within the category. With the exception of pentachloropyridine, which is calculated to favor partition to air, the single chemicals are calculated to distribute relatively evenly among water, air, and soil, with very little partitioning to sediment.

Thus, sufficient data are available for prediction of physicochemical properties for the category, and no further testing is needed.

Table 3. Comparison of Biodegradation Data for Category Members

Category Member	ThOD (mg/g substance)	BOD/COD	Biodegradation
A. 2176-62-7	0.64	ND	ND
B. 1817-13-6	ND	ND	Not readily biodegradable[1]
C.69045-78-9	ND	COD: 0.44 mg/mg BOD: 12% within 28 days	Not readily biodegradable[1]
D.17824-83-8	ND	ND	Not readily biodegradable[1]
E. 2402-79-1	ND	ND	50% within 95 days
F. 68412-40-8	ND	ND	ND
G. 70024-85-0	ND	ND	ND

ND = Not Determined
[1]Calculated value.

Table 3 documents a variety of biodegradation type data for chemicals within the category. Results from the studies consistently indicate a low potential for ready biodegradability, whether calculated or empirical data are considered. Thus, sufficient data are available for prediction of biodegradation for the category, and no further testing is needed.

Table 4. Comparison of Ecotoxicity Data (LC_{50}/EC_{50}) for Category Members			
Category Member	Acute Fish (mg/l)	Acute Invertebrate (mg/l)	Alga (mg/l)
A. 2176-62-7	0.47 (fathead minnow, 96 h) 1.23 (Emerald shiner, 72 h)	1.8 (shrimp, 43 h) >6 (soft-shell clam, 96 h) ND (*Tetrahymena pyriformis*) 0.4 ng/l[1]	2.03 (*Selenastrum capricornutum*, 96 h)
B. 1817-13-6	ND	0.1 mg/l[1]	ND
C.69045-78-9	>99 (fathead minnow, 96h)	>100 (*Daphnia magna*, 48 h) 0.1 mg/l[1]	ND
D.17824-83-8	26.0 (fish, calculated)	27.4 (*Daphnia sp.*, calculated by EPA programs) 0.002 mg/l[1]	18.1 (alga, calculated)
E. 2402-79-1	1.5 (rainbow trout, 96 h)	2.05-2.14 (*D. magna*, 48 h)	8.8-14.1 (*S. capricornutum*, 120 h)
F. 68412-40-8	ND	ND	ND
G. 70024-85-0	ND	ND	ND
ND = Not Determined [1]Calculated value, TOPKAT® QSAR prediction for *Daphnia sp.*			

Table 4 documents ecotoxicity data for chemicals within the category. The aquatic toxicity of the single chemicals within this category appears to decrease with decreasing chlorination of the pyridine ring and increasing size of side chains to the pyridine ring. The most sensitive empirically derived endpoint for aquatic toxicity is that of the acute fish toxicity for pentachloropyridine, 0.47 mg/l, indicating a high level of toxicity. TOPKAT® prediction for invertebrates for this material is also low, 0.38 ng/l, as are TOPKAT predictions for other category members. Thus, all chemicals within the category may be considered potentially highly toxic to aquatic organisms. Considering that further testing would result in no increase in warnings, no further testing is needed.

Table 5. Comparison of Animal Toxicity Data for Category Members							
Category Member	Acute Toxicity				Repeated Dose Toxicity	Genetic Toxicity: In Vitro and In Vivo	Development Toxicity
	Acute Oral Toxicity	Dermal Irritation	Ocular Irritation	Dermal Sensitization			
A. 2176-62-7	•435 mg/kg (male rat, gavage) •126-1000 mg/kg (female rat, diet)	•Slight to moderate irritation (rabbit, 1 24-h application) •Burns (rabbit, repeated 24 h applications)	•Slight conjunctival irritation, resolved within 24 h	•Sensitizing (split adjuvant method)	•Kidney and liver effects (rat, 90-day, diet, NOAEL=10 mg/kg/day) •No effects (rat, 16-day, inhalation for 6 h, NOAEL=>1 ppm)	•Negative in bacterial reverse mutation assay (S. typhimurium TA98, TA100, TA1535, TA1537; E. coli WP2uvrA •Negative in rat lymphocyte chromosomal aberration assay •Negative in cytogenetic assay in mouse bone marrow	•Reduced fetal weight at maternally toxic dose levels (rat, developmental toxicity, gavage)
B. 1817-13-6	•1000-2000	• Slight to marked	•Moderate conjunctival	ND	•Liver effects (rat, 9-day,	ND	ND

	mg/kg (male rat, gavage)	irritation (rabbit, 1 24-h application) •Burns (rabbit, repeated 24 h applications)	and iridial irritation, slight corneal opacity, resolved within 48 h		inhalation for 6 h, NOAEL=0.32 ppm) •Liver effects (mouse, 9-day, inhalation for 6 h, NOAEL=0.32 ppm)		
C.69045-78-9	•500-1000 mg/kg (male rat, gavage)[1]	• Slight to moderate irritation (rabbit, 1 24-h application) •Burns (rabbit, repeated 24 h applications)	•Slight conjunctival irritation, very slight iridial irritation and corneal opacity, resolved within 48 h	•Sensitizing (modified Maguire method)	•Liver effects (rat, 2-week, inhalation for 6 h, NOAEL=1 ppm) •Liver effects (mouse, 2-week, inhalation for 6 h, NOAEL=1 ppm)	ND	ND
D.17824-83-8	•1000-2000 mg/kg (female rat, gavage) [2]	• Slight to moderate irritation (rabbit, 1 24-h application) •Burns	•Slight to moderate conjunctival irritation, resolved within 7 days[2]	ND	ND	ND	ND

		(rabbit, repeated 24 h applications)					
E. 2402-79-1	•1414 mg/kg (male rat, gavage) •1182 mg/kg (female rat, gavage) [3]	• Slight irritation (rabbit, repeated 24-h applications)	•Very slight conjunctival irritation, resolved within 1 h	•Not sensitizing (modified Maguire method)	•Kidney effects in males (rat, 91-day, diet, NOAEL=100 mg/kg/day) – hyaline droplet formation	•Negative in bacterial reverse mutation assay (S. typhimurium TA98, TA100, TA1535, TA1537 •Negative in mouse micronucleus assay	•No effects on offspring even at maternally toxic levels (rat, developmental/reproductive toxicity screen, IP injection)
F. 68412-40-8	ND	ND	ND	ND	ND	ND	ND
G. 70024-85-0	ND	ND	ND	ND	ND	ND	ND

ND = Not Determined
[1]An acute inhalation toxicity study also exists: LC50 > 114 ppm (male rat, 6 h)
[2]Single human exposures in an industrial setting have resulted in slight respiratory irritation, slight to moderate conjunctival irritation and slight to severe corneal injury.
[3]An acute inhalation toxicity study also exists: LC50 > 6300 ppm (male rat, 7 h)

Table 5 documents animal toxicity data for chemicals within the category.

Acute Toxicity: All single chemicals within the category are low to moderate in acute oral toxicity, with the lowest LD50 recorded being that for pentachloropyridine (2176-62-7) at 435 mg/kg in male rats via gavage. A range of values for the same chemical, 126-1000 mg/kg in female rats, encompasses the male rat value, but testing was conducted via a less commonly used route of exposure, inclusion in diet. Because no analyses of diet were conducted for this study, there is some uncertainty about calculated dose and therefore is considered valid with restrictions. However, the range specified still falls within the range of moderate toxicity. Other single chemicals in the category have oral LD50 values in the range of 500-2000 mg/kg via gavage. In addition, two single chemicals within the category, 2-chloro-5-trichloromethylpyridine (69045-78-9) and 3,4,5,6-tetrachloro-2-pyridine carbonitrile (17824-83-8) have inhalation LC50 values indicating a low to moderate level of toxicity consistent with the oral route of exposure. Results of QSAR calculations using TOPKAT® and DEREK® (Table 5) support the categorization of oral toxicity as moderate.

With regard to dermal irritancy potential, single chemical category members produce slight to moderate irritation with a single prolonged (24-hour) application, while repeated applications result in burns, with the single exception of 2,3,5,6-tetrachloropyridine, which did not produce burns upon repeated application. Results of QSAR calculations using TOPKAT® and DEREK® (Table 5) support the categorization of irritancy potential as slight to moderate.

Similar patterns for single chemical category members are seen in ocular irritancy studies, in which chemicals produce slight to moderate irritancy with no evidence of permanent impairment of vision. Results of QSAR calculations using TOPKAT® and DEREK® (Table 5) support the categorization of irritancy potential as slight to moderate.

Of the single chemical category members tested for potential to produce dermal sensitization, two (pentachloropyridine, 2176-62-7, and 2-chloro-5-trichloromethylpyridine, 69045-78-9) have produced evidence of dermal sensitization, while a third, 2,3,5,6-tetrachloropyridine, was negative in dermal sensitization testing under a modified Maguire method. Thus, category members should be regarded as having some level of potential to cause dermal sensitization. Results of QSAR calculations using TOPKAT® and DEREK® (Table 5) support the proposition of positive dermal sensitization potential.

With regard to acute toxicity, sufficient data exist to allow prediction of toxicity for category members, and thus no further testing is needed.

Repeated Dose Toxicity: Single chemical category members tested demonstrate effects on kidney and liver in rats and mice via both inhalation and dietary routes of administration in tests ranging from 9 to 90 days. The NOAEL for repeated dose toxicity for the various members of this category is consistent, and within a relatively narrow range (0.32 to 1 ppm for inhalation studies, 10-100 mg/kg/day for dietary studies), based on a composite evaluation of all the repeated dose toxicity studies. These repeated dose toxicity studies have also reported a similar and common profile of target organs. Thus, the results of the collection of sub-chronic and chronic studies conducted on these substances are consistent and can be regarded as offering a true picture of repeated dose toxicity. With regard to repeated dose toxicity, sufficient data exist to allow prediction of toxicity for category members, and thus no further testing is needed.

Genetic Toxicity: Single chemical category members tested via both *in vitro* and *in vivo* genetic toxicity test methods have consistently produced negative results, indicating that these materials lack potential for genetic toxicity. Tests conducted include Ames assay both with and without metabolic activation, rat lymphocyte chromosomal aberration assay, mouse bone marrow cytogenicity assay, and mouse micronucleus assay. Results of QSAR calculations using TOPKAT® and DEREK® (Table 5) produce mixed results for mutagenicity potential, and thus must be considered carefully. With regard to genetic toxicity, sufficient data exist to allow prediction of toxicity for category members, and thus no further testing is needed.

Developmental Toxicity: Two category members, pentachloropyridine (2176-62-7) and tetrachloropyridine (2402-79-1), have been tested for potential to cause developmental toxicity. Pentachloropyridine produced evidence of reduced fetal weight only at maternally toxic dose levels, while tetrachloropyridine produced no evidence of developmental effects even at maternally toxic dose levels in a Chernoff test. As a conservative estimate, category members should be regarded as having potential to cause fetotoxicity at maternally toxic dose levels. Results of QSAR calculations using TOPKAT® and DEREK® (Table 5) support the extrapolation of ability to cause some level of developmental toxicity for at least one category member, 2-chloro-5-trichloromethylpyridine (69045-78-9). With regard to developmental toxicity, sufficient data exist to allow prediction of toxicity for category members, and thus no further testing is needed.

Table 5. Comparison of TOPKAT® and DEREK® QSAR Preditions for Category Members[a]								
Endpoints of Interest	A. 2176-62-7		B. 1817-13-6		C.69045-78-9		D.17824-83-8	
	T	D	T	D	T	D	T	D
Rat Oral LD50	77.8 mg/kg	NA	48.4 mg/kg	NA	195.6 mg/kg	NA	66.4 mg/kg	NA
Dermal Irritancy	+	-	-*	-	-*	-	-	-
Ocular Irritancy	+, Mild*	-	+. Moderate*	-	+. Moderate*	-	?	-
Dermal Sensitization	-*	+	+, Mild/Moderate*	-	+, Mild/Moderate*	-	+, Mild/Moderate*	+
Mutagenicity[b]	-	-	+*	+	+	+	+	-
Developmental Toxicity	-	-	-	-	+	-	-	-
Log P/Low KoW	4.06	NA	3.15	NA	2.81	NA	3.08	NA
Aerobic Biodegradability	-	NA	+	NA	-	NA	-	NA
Fathead minnow LC50	@	NA	@	NA	@	NA	@	NA
Daphnia LC50	381.6 ng/l	NA	64.1 µg/l	NA	515.9 µg/l	NA	1.7 µg/l	NA

[a]Because two of the category members (E. 68412-40-8 and F. 70024-85-0) are process streams for which component levels vary, no QSAR analysis could be conducted.
[b]TOPKAT® predicts results for the Ames' mutagenicity assay, while DEREK® predicts general mutagenicity results.
T = TOPKAT® results.
D = DEREK® results.
NA = Value not computed by the specified QSAR program.
+ = Probable
- = Improbable
? = Indeterminate
* = Accuracy can not be determined
@ = Error: Endpoint cannot be computed. No suitable submodel.

4. Conclusion

This test plan is expected to provide adequate data to characterize the human health effects and environmental fate and effects endpoints under the Program.

Evaluation of the chemicals in this category leads to the conclusions that [1] data currently exist to adequately represent the toxicological and ecological profile of major portions of this category, [2] there is a concurrence and similarity among the existing data for the various HPV/SIDS endpoints, supporting a single, continuous category, and [3] extrapolation from available data from previously conducted studies can be used to adequately represent most of the HPV/SIDS endpoints for individual members of the category. In addition, the nature of the chemical; the manner in which the chemical is manufactured, distributed, processed and used, the product stewardship measures taken to prevent exposure; and existing human/environmental data, indicate that our workers, the public and the environment are well protected from exposure to the chemicals within this category, and no further testing is needed.

REFERENCES

U.S. EPA . 1999. The use of structure-activity relationships (SAR) in the High Volume Chemical Challenge program, OPPT, EPA.

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I U C L I D

Data Set

Existing Chemical	:	ID: 69045-78-9
CAS No.	:	69045-78-9
Product name	:	2-Chloro-5-trichloromethylpyridine

Producer related part

Company	:	Dow Chemical, TERC
Creation date	:	21.09.2004

Substance related part

Company	:	Dow Chemical, TERC
Creation date	:	21.09.2004
Status	:	
Memo	:	
Printing date	:	08.12.2005
Revision date	:	
Date of last update	:	08.12.2005
Number of pages	:	39
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	manufacturer
Name	:	Dow Agrosciences PLC
Contact person	:	
Date	:	
Street	:	9330 Zionsville Road
Town	:	46268 Indianapolis, IN
Country	:	United States
Phone	:	(+1) 317-337-3890
Telefax	:	(+1) 317-337-4444
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

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1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	
Substance type	:	organic
Physical status	:	solid
Purity	:	ca. 90 - 100 % w/w
Colour	:	White
Odour	:	
Reliability	:	(1) valid without restriction

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1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= 52 - 54 °C
Sublimation	:	
Method	:	other
Year	:	1984
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

22.09.2004 (1)

2.2 BOILING POINT

Value	:	= 245 °C at
Decomposition	:	
Method	:	other
Year	:	2003
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Calculated using EPA's programs.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

22.09.2004 (2)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= .014 hPa at 25 °C
Decomposition	:	
Method	:	other (calculated)
Year	:	2003
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Value calculated using EPA's programs.
Source	:	The Dow Chemical Company, Midland, MI.

22.09.2004 (2)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	= 3.35 at 25 °C
pH value	:	
Method	:	other (calculated)
Year	:	2003

GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Value calculated using EPA's programs.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
22.09.2004 (3)

Partition coefficient : octanol-water
Log pow : = 3.39 at °C
pH value :
Method : other (calculated)
Year : 1983
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Log Kow calculated from water solubilty of 99 mg/l.
Remark : GLP not compulsory at time study was performed.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
Study conducted in accordance with generally accepted scientific principles.
23.09.2004 (4)

Partition coefficient : water - air
Log pow : < 4 at 25 °C
pH value :
Method : other (measured)
Year : 1983
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : A determination was made for the air/water partition coefficient by air sparging one liter of solution at approximately 450 ml/min for five days. Loss of total carbon (TC) was monitored with a Beckman 915B Total Carbon Analyzer.
Remark : GLP not compulsory at time study was performed.
Result : Air/Water Partition Coefficient: <10-4 (by TC analysis)

Fraction of concentration remaining: 25% removal in 96 h
100% within 120 h
Source : The Dow Chemical Company, Midland, MI.
Reliability : (2) valid with restrictions
Study conducted in accordance with generally accepted scientific principles.
23.09.2004 (4)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 99 mg/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other

Year : 2003
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Value calculated using EPA's programs.
Remark : Dissociation Constant: Not applicable. Does not ionize within environmentally relevant pH ranges.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (2) valid with restrictions
08.12.2005 (5)

Solubility in : Water
Value : = 99 mg/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other
Year : 1983
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Water solubility was determined by the nephelometric technique.
Remark : GLP not compulsory at time study was performed.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
23.09.2004 (4)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

Result : no oxidizing properties
Method : other
Year : 2003
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Not Applicable. Not expected to have significant oxidizing or reducing potential.

Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
22.09.2004

2.12 DISSOCIATION CONSTANT

Acid-base constant : N/A
Method : other
Year : 2003
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Not applicable. Does not ionize within environmentally relevant pH ranges.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
22.09.2004

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

INDIRECT PHOTOLYSIS

Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	= .0000000000000477 cm³/(molecule*sec)
Degradation	:	= 50 % after 224 day(s)
Deg. product	:	
Method	:	other (calculated)
Year	:	2005
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Values calculated using EPA's programs.
Result	:	The rate constant for the vapor phase reaction with photochemically produced hydroxyl radicals is estimated to be 0.0477E-12 cm3/molecule-sec at 25C; which corresponds to a tropospheric half-life of 224.275 days (12-hr day; 1.5E+06 OH/cm3).
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

08.12.2005 (6)

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	
Air	:	17.9 % (Fugacity Model Level I)
Water	:	27.1 % (Fugacity Model Level I)
Soil	:	53.8 % (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	83.3 % (Fugacity Model Level II/III)
Method	:	other
Year	:	2005
Remark	:	Values calculated using EPA's programs.
Source	:	The Dow Chemical Company, Midland, MI.
Attached document	:	2C5TCMpyridineFugacity.doc
Reliability	:	(1) valid without restriction

08.12.2005 (7)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Deg. product :
Method : other
Year : 2005
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Values calculated using EPA's programs.
Result : Material is estimated not to biodegrade fast using a linear and non-linear SAR method, and not to be readily biodegradable using a MITI linear and non-linear SAR method. Ultimate and primary biodegradation is estimated to occur in 2.88 weeks-months.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
07.09.2005 (8)

3.6 BOD5, COD OR BOD5/COD RATIO

COD
Method : other
Year : 1983
COD : mg/g substance
GLP : no

Method : HACH COD System
Remark : GLP not compulsory at time study was performed.
Result : COD = 0.44 p/p.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
Test method is accepted by EPA.
23.09.2004 (4)

BOD5
Method :
Year : 1983
Concentration : related to
BOD5 : mg/l
GLP : no

Method : Biochemical Oxygen Demand (BOD) tests were run using industrial (The Dow Chemical Company's Michigan Division) wastewater treatment plant secondary effluent and the Midland City Municipal Wastewater Treatment Plant secondary effluent (prior to chlorination) as seeds. These seeds were filtered through Whatman 114V filter paper and used at ratios of 10 ml filtrate/l of dilution water.
Remark : GLP not compulsory at time study was performed.
Result :

	Industrial		Municipal	
Days	BOD	% ThOD	BOD	% Thod
5	0.04	4	0.03	3
10	0.05	5	0.05	5
20	ND	-	0.04	4
28	0.12	12	0.02	2

A glucose/glutamic acid standard indicated viable seed.

Source : The Dow Chemical Company, Midland, MI.
Reliability : (2) valid with restrictions
Study conducted in accordance with generally accepted scientific principles.

23.09.2004 (4)

3.7 BIOACCUMULATION

Species : other: fish
Exposure period : at °C
Concentration :
BCF : = 153
Elimination :
Method : other
Year : 1983
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : BCF calculated from log Kow.
Remark : GLP not compulsory at time study was performed.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction

23.09.2004 (4)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	> 99 measured/nominal
Limit test	:	
Analytical monitoring	:	no
Method	:	other
Year	:	1983
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Dilution Water
The laboratory water supply used as dilution and culture water for the Environmental Sciences Research Laboratory is pumped from an intake approximately 1.6 km. (1 mi) off Whitestone Point in upper Saginaw Bay, Lake Huron, Michigan. This Lake Huron water is carbon filtered and U.V. irradiated prior to use. Routine analyses of the laboratory water were conducted before and during this testing. The fact that the test organisms were under successful culture in this water throughout this test period demonstrates the satisfactory quality of the dilution water.

A range-finding test was then set with five concentrations in a geometric series at a ratio of 1:0.3163 (half-decade intervals) ranging from 0.99 mg/L to 99.9 mg/L. This test indicated that the LC50 would be greater than 100 mg/L. Therefore, a definitive test was not run as a well-defined LC50 could not accurately be determined setting test concentrations above the soluble concentration of the test material in water.

A stock solution was prepared by weighing 0.50 grams of the test material into a 50 mL volumetric flask on a top-loader balance (Mettler PL-3000) and diluting to volume with acetone. The test concentrations were then prepared from acetone dilutions of the stock by delivering the toxicant in 0.1 mL acetone into 200 mL dilution water in 250 mL test beakers. Acetone was used as a carrier to insure maximum dispersion of the test material in water and did not exceed the maximum limit (0.5 mL acetone/L dilution H20) indicated by the ASTM Standard Practice.

Each test concentration was set in triplicate, and 10 first instar water fleas, Daphnia magna Straus, were added to each beaker. Exposure period was 48 hours. A triplicate set of dilution water controls and acetone controls was also prepared. A fourth beaker was also set with daphnids for the high, medium, low and control test concentrations. These latter replicate vessels were used only for pH, dissolved oxygen, and temperature measurements. All test beakers were placed in a temperature-controlled environmental chamber set to maintain 20 ± IOC. Photoperiod timers were set to provide 16 hours light and 8 hours of darkness. Death was the effect criterion and was defined as no movement or response to gentle prodding. Dead water fleas were not removed, there was no feeding during the test, and mortalities were recorded daily except those test concentrations and controls set with a 4th test beaker.

Remark : GLP not compulsory at time study was performed.

Result :

No-Mortality Concentration	0.99 mg/L
Lowest Partial-Mortality Concentration	9.9 mg/L
100%-Mortality Concentration	>99.9 mg/L a
Acetone Control Mortality	0%
Dilution Water Control Mortality	0%

Dissolved Oxygen Concentration (0-48 Hours) 98-102% satur.
pH (0-48 Hours) 8.1-8.2
Temperature (0-48 Hours) 19.6ºC-20.4ºC

a Highest concentration set in definitive test - limit of solubility

The raw data and statistical calculations indicate that an LC50 value could not be calculated.

Source : The Dow Chemical Company, Midland, MI.
Reliability : (2) valid with restrictions
Study conducted in accordance with generally accepted scientific principles.

23.09.2004 (4)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : > 100 measured/nominal
Analytical monitoring : no
Method : other
Year : 1983
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Dilution Water
The laboratory water supply used as dilution and culture water for the Environmental Sciences Research Laboratory is pumped from an intake approximately 1.6 km. (1 mi) off Whitestone Point in upper Saginaw Bay, Lake Huron, Michigan. This Lake Huron water is carbon filtered and U.V. irradiated prior to use. Routine analyses of the laboratory water were conducted before and during this testing. The fact that the test organisms were under successful culture in this water throughout this test period demonstrates the satisfactory quality of the dilution water.

Testing procedures were based upon the guidelines in the standard operating procedure, "Static Acute Fish Toxicity Test 4" and the procedures recommended by the ASTM Subcommittee on Safety to Aquatic Organisms.

A definitive test was set with nine concentrations in a geometric series at a ratio of 1:0.85 ranging from 27.2 mg/L to 100 mg/L. The fathead minnows, Pimephales promelas Rafinesque, used in this test were laboratory reared (approximately 71 days old) with the designated Lot No. FM-021582-LR. No fish mortalities were observed in this 96-hour static acute toxicity test at those nominal test concentrations set up to and including 100 mg/L, therefore, no further definitive tests were run as an LC50 could not be determined setting test concentrations above the soluble concentration of the test material in water. A stock solution was prepared by weighing 20.0 grams of the test material into a 50 mL volumetric flask on a top-loader balance (Mettler PL-3000) and diluting to volume with acetone. The test concentrations were then prepared from ace- tone dilutions of the stock by delivering the toxicant in 5.0 mL acetone into the test vessels. Acetone was used as a carrier to ensure maximum dispersion of-the test material in water and did not exceed the maximum limit indicated by the ASTM Standard Practice (0-5 mL acetone/L dilution water).

Test vessels were Pyrex cylindrical battery jars approximately 22 cm deep by 24.5 cm in diameter and were placed in constant-temperature water troughs set to maintain 17 + 1ºC.

For acclimation, each vessel received eight liters of dilution water to which 10 fish were indiscriminately added. Fish were not fed during acclimation or testing. Gentle aeration proceeded for an acclimation period of 4-8 hours prior to initiation of toxicant exposure by termination of aeration and addition of the 2 liters of premixed test solution to each test vessel. A water control and an acetone control (0.5 mL acetone/liter dilution water) received a similar quantity of water without test material. Final volume in each vessel was therefore ten liters. Photoperiod timers were set to provide 16 hours light and 8 hours of darkness in both culture and testing areas. Fish were exposed to test material for 96 hours.

The primary effect criterion was defined as lack of movement or response to gentle prodding. Every 24 hours, mortality was recorded and the dead fish removed. Dissolved oxygen concentration, pH and temperature were recorded from representative test vessels daily. At test termination, acetone control fish were weighed and measured to estimate loading rate and size variation.

Remark : GLP not compulsory at time study was performed.

Result : Fathead Minnow 96-Hour Static Acute Toxicity Test

No-Mortality Concentration 100 mg/L
100%-Mortality Concentration >100 mg/L a
Acetone Control Mortality 0%
Dilution Water Control Mortality 0%
Dissolved Oxygen Concentration (0-48Hours) 102.0-74.0% satur.
(48-96 Hours) 84.0-72.0% satur.
pH (0-96 Hours) 6.8-8.1 Temperature (0-96 Hours) 16.6ºC-17.6ºC

Test Fish:
Average Weight 0.21 g
Standard Length Mean 2.33 cm
Standard Length Range 1.70-2.80 cm
Average Loading 0.21 g/L

a Highest concentration set in definitive test - limit of solubility

The raw data and statistical calculations indicate that an LC50 value could not be calculated.

Source : The Dow Chemical Company, Midland, MI.

Reliability : (2) valid with restrictions
Study conducted in accordance with generally accepted scientific principles.

23.09.2004 (4)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : = 500 - 1000 mg/kg bw
Species : rat
Strain : Sprague-Dawley
Sex : male
Number of animals : 15
Vehicle : other: corn oil
Doses : 130, 250, 500, 1000, 2000 mg/kg
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Young adult male Sprague-Dawley rats were fasted overnight. They were administered the material as a 10% solution in corn oil at a dose volume of 10 ml/kg bw at dose levels of 130, 250, 500, 1000, or 2000 mg/kg bw. Animals were observed closely for two weeks, then submitted for pathological examination. All animals which died prior to scheduled necropsy were also submitted for pathological examination. Body weights were recorded on the day of treatment (Study Day 0), and Study Days 1, 8, and 15.
Remark : GLP not compulsory at time study was performed.
Result : Two of three rats from each of the 1000 or 2000 mg/kg dose groups died prior to scheduled necropsy. All other rats survived the observation period. All rats exhibited lethargy; rats given 500 mg/kg had rough hair coats, while rats given 1000 or 2000 mg/kg had diarrhea, palpebral closure, and shallow breathing. All clinical signs resolved within 2 days of treatment in surviving rats. All surviving rats gained weight during the observation period. Rats which died prior to study termination had non-specific findings at necropsy, including pale livers, red foci in the stomach, red urine, and darkened kidneys. No other alterations were observed at necropsy.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (2) valid with restrictions
Study conducted in accordance with generally accepted scientific principles.

22.09.2004 (4)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Value : > 11.4 ppm
Species : rat
Strain : Fischer 344
Sex : male
Number of animals : 6
Vehicle : other: ambient air
Doses : 11.4 ppm
Exposure time : 6 hour(s)
Method : other
Year : 1986
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Animals

Male Fischer 344 (F-344) rats, 6-8 weeks of age were obtained from Charles River Breeding Laboratories, Inc., Kingston, NY. The animals were 9 weeks old when exposed to the test material. Selection of this species was based on a variety of considerations including hardiness, low incidence of respiratory disease and historical control data. Upon arrival at the laboratory,l the health status of the animals were determined by the laboratory veterinarian. The animals were acclimated to the laboratory for at least one week prior to exposure. Animals were fed Purina Certified Rodent Chow (Ralston Purina Co., St. Louis, MO) and water ad libitum except during exposure. During the acclimation process, rats were weighed. Animals at the extremes of the weight distribution were discarded from the study and the remaining animals were randomized by weight into respective groups of 6 animals/group. One group of 6 rats was used for this study. Animals were individually identified with a metal ear tag. Prior to and after exposure, animals were housed in rooms designed to control temperature (72'F), relative humidity (50%) and light cycle (12 hours light and 12 hours dark). Animals were group housed prior to exposure and singly housed during the 2-week post-exposure period.

Exposure Atmosphere and Chambers
Vapors of 2-chloro-5-trichloromethylpyridine were generated by using a modification of the glass J-tube method (Miller et al., 1980). The J-tube was filled with a mixture of solid test material and 6 mm glass beads. Compressed air was heated (68-82'C) with a flameless heat torch (Master FHT-4) to the minimum extent necessary to volatilize the test material. The air passing through the J-tube was diluted with the main chamber airstream prior to entering the chamber. The chamber airflow was maintained at approximately 30 liters/minute. Animals were exposed to the test material in 157 liter stainles5 steel and glass Rochester-type chambers. A group of 6 male rats was exposed to the maximum practically attainable concentration of 2-chloro-5-trichloro- methylpyridine in the air for 6-hours.

Atmosphere Analysis
The nominal concentration of the test material in the chambers was determined based on the total amount of test material utilized versus the total airflow through the chambers during the exposure period. The analytical concentration of 2-chloro-5-trichloromethylpyridine was determined 3 times during the exposure period using a gas chromatograph (Varian 2400, Varian Aerograph, Walnut Creek, CA) with a flame ionization detector. A 6 ft x 1/8 inch stainless steel column packed with 10% SP-2100 on 100/120 mesh SP-2100 was used to separate the test material from carbon tetrachloride. The gas chromatographic conditions were as follows: Nitrogen (carrier) flow = 70 ml/min, hydrogen flow = 47 ml/min, airflow = 300 ml/min, injection temp. 268'C, column temp. = 1920C, and detector temp. = 262'C. Liquid standards of the test material were prepared in carbon tetrachloride. The chamber concentration of 2-chloro-5-trichloromethylpryidine was determined by drawing measured volumes of chamber air samples through an impinger containing carbon tetrachloride. The concentration of 2-chloro-5-trichloromethylpyridine in the trapped sample was determined by interpolation from known standards. The analytical system was evaluated with at least one standard prior to the exposure.

The temperature and relative humidity in the chamber was controlled by a system designed to maintain temperature and relative humidity at 70'F and 50%, respectively. Relative humidity and minimum and maximum temperature for the 6-hour exposure period were recorded at the end of the exposure.

Observation and Criteria of Response

Animals were weighed and examined prior to exposure to the test material. All animals were observed during the exposure period and at least daily during the two-week post-exposure period for any exposure- related effects. All surviving animals were weighed on the first day after exposure and approximately twice per week during the two-week post-exposure period. Animals were submitted for gross necropsy at the end of this two-week period.

Statistics

Descriptive statistics (mean and standard deviations) were used to describe animal body weights.

1Accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

Result : Rats were exposed to 11.4 ppm of 2-chloro-5-trichloromethylpyridine for 6 hours (Table 1). This was the maximum practically attainable concentration. At this concentration, vaporized test material recrystalized in the delivery tube but not in the chamber. The nominal concentration was much higher than the analytical concentration and was most likely due to recrystalization of test material in the delivery tube.

No clinically visible effects were observed during the exposure or 2-week post-exposure period which were considered to be exposure- related. Rats exposed to 11.4 ppm 2-chloro-5-trichloromethylpyridine gained weight throughout the 2-week post-exposure period (Table 2). Gross pathologic examination of these animals two weeks after exposure to the test material did not reveal any lesions.

Under the conditions of this study, no adverse effects were observed which were attributed to exposure to 2-chloro-5-trichloro-methylpyridine.

Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
22.09.2004 (4)

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species : rabbit
Concentration : .5 g
Exposure : Occlusive
Exposure time : 24 hour(s)
Number of animals : 2
Vehicle : water
PDII :
Result :
Classification :
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method	:	A male rabbit was prepared by shaving the hair from the entire abdomen with a straight razor and barber soap. The animal was then rested for several days to allow any abrasions to heal completely and to be sure skin was suitable for use. Two sites on the abdomen were used for applications: one intact, the other cross-hatched with a sharp hypodermic needle to penetrate the stratum corneum but not to produce more than a trace of bleeding. Ten applications under dry conditions were made to the intact abdominal site over a period of 14 days. Three consecutive daily applications were made to the abraded site. Both abdominal sites were covered with 1X1 cotton pads and held place with a single cotton cloth taped to remaining body hair. Applications were discontinued upon production of a substantial skin burn, or if the animal died. A second male rabbit was treated similarly, except that applications were made to moistened skin, rather than dry.
Remark	:	GLP not compulsory at time study was performed.
Result	:	Prolonged and repeated contact with the material on dry skin resulted in moderate redness, slight edema, slight exfoliation and a superficial burn on the intact application site. Prolonged and repeated contact on moistened skin resulted in moderate to marked redness, very slight (intact) to moderate (abraded) edema, very slight exfoliation and, after 3 applications, moderate burns.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(2) valid with restrictions Study conducted in accordance with generally accepted scientific principles.

22.09.2004 (4)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 other: g
Exposure time	:	1 hour(s)
Comment	:	other: one eye rinsed after 3 minutes, the other unrinsed
Number of animals	:	1
Vehicle	:	none
Result	:	
Classification	:	
Method	:	other
Year	:	1981
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Both eyes of a male New Zealand White rabbit were stained with 5% fluorescein dye and examined for evidence of injury or alterations. The rabbit was then allowed to rest for 24 hours before test. 0.1 g of the material were introduced into the right eye. The eye was washed within 30 seconds for 2 minutes in a flowing stream of tepid water. 0.1 g of material were introduced in a similar fashion to the left eye, but this eye was left unwashed. Immmediately after instillation into each eye, the rabbit was examined for signs of discomfort. Within 2-3 minutes after the unwashed eye was treated, each eye was observed for conjunctival and corneal response. Similar observations were made on both eyes at 1 hour, 24 hours, 48 hours, and 7 days post-treatment. Examinations were conducted both with and without fluorescein dye.
Remark	:	GLP not compulsory at time study was performed.
Result	:	Instillation into the rabbit eye resulted in severe discomfort, slight

conjunctival redness, very slight reddening of the iris, and very slight corneal haziness. All signs of irritation were absent 48 hours after exposure. Similar results were obtained in both the washed and the unwashed eye.

Source : The Dow Chemical Company, Midland, MI.

Reliability : (1) valid without restriction
Study conducted in accordance with generally accepted scientific principles.

22.09.2004 (4)

5.3 SENSITIZATION

Type : other: Modified Maguire method
Species : guinea pig
Concentration : 1st: Induction 10 % semiocclusive
2nd: Induction 10 % semiocclusive
3rd: Induction 10 % semiocclusive
Number of animals : 10
Vehicle : other: Dowanol DPM:Tween 80 9:1
Result : sensitizing
Classification :
Method : other
Year : 1983
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : TEST ANIMALS

The skin sensitization test was conducted on male Hartley albino guinea pigs (Charles River Breeding Laboratories Inc., Kingston, New York). All animals were maintained on a 12-hour photocycle in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care. They were supplied with commercial laboratory chow (Ralston Purina Company, St. Louis, Missouri) and water ad libitum. All guinea pigs were acclimated to the laboratory environment at least 1-week prior to testing, and were housed 5/cage. Each guinea pig was uniquely identified by a metal eartag and was also color coded for easier identification during the study.

SKIN SENSITIZATION TEST

The guinea pig sensitization method used is a modification of the method of Maguire (1973). The test material was applied as a 10% solution in DOWANOL DPM/Tween 80 (9:1). Ten guinea pigs received 4 applications of the test material dilution in 7 days during the insult phase of testing. An additional group of 10 guinea pigs received DER 331 epoxy resin as a 10% solution in DOWANOL DPM/Tween 80 (9:1). The epoxy resin is known to be a skin sensitizer and served as a positive control. Each insult application consisted of 0.1 ml of the test material or of the positive control resin and was applied on a gauze square held in place and covered with adhesive tape. The first insult application was allowed to remain in place for two days, then removed and a second application of 0.1 ml was made. At the time of the third application, 0.2 ml total of Freund's Adjuvant (Bacto-Adjuvant complete, H37RA DTFCO Laboratories, Detroit, Michigan) was injected intradermally adjacent to the insult site. On the second day after this application, the patch was removed and a fresh patch of 0.1 ml of the material was applied. The test patch was removed two days later and the animals allowed to rest for two weeks. Each time the insult patches were removed, observations of primary irritation effects were made and recorded. After a two-week rest period, both flanks of the animals were

		clipped and challenged with the test solution on one side and the appropriate solvent on the other. The challenge applications were not covered. Skin response at these sites was recorded at 24 and 48 hours after application. Any animal showing redness and/or edema at the test solution challenge sites was noted as a positive responder.
Remark	:	GLP not compulsory at time study was performed.
Result	:	A positive response indicative of sensitization (slight to moderate redness) was observed on 10 of 10 guinea pigs receiving DER 331. The test material also indicated a positive sensitization response in 8 of 10 guinea pigs. Therefore, as a 10% solution in DOWANOL DPM/Tween 80 (9:1), this material should be considered as possessing significant potential as a human skin sensitizer.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(2) valid with restrictions Study conducted in accordance with generally accepted scientific principles.

22.09.2004 (4)

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	inhalation
Exposure period	:	6 h/day
Frequency of treatm.	:	5 days/week for 2 weeks
Post exposure period	:	
Doses	:	0.1, 1.0, 10 ppm
Control group	:	yes, concurrent vehicle
NOAEL	:	= 1 ppm
Method	:	EPA OPP 82-4
Year	:	1987
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Study Design. Groups of five mice/sex were exposed for 6 hours/day, 5 days/week to target concentrations of 0, 0.1, 1.0, or 10 ppm for two weeks (nine exposures interrupted by one weekend). On the day following the last exposure, each surviving animal was necropsied.

Urine and blood were obtained for selected clinical pathologic evaluations. Major organs were weighed and tissues were saved in neutral, phosphate-buffered 10% formalin for subsequent examination. The highest targeted exposure level, 10 ppm, produced the maximum practically attainable concentration in this study. The lowest exposure level, 0.1 ppm, was chosen to assess a no-observed-effect level. The 1.0 ppm exposure level was chosen to aid in defining a dose response. The study was initiated on May 5, 1986 and mice were necropsied on May 16, 1986.

Test Species and Husbandry. Seven-week old B6C3Fl mice (Charles River Breeding Laboratory, Portage, Michigan) were purchased for the study. Extra animals were ordered to ensure that a sufficient number of animals of acceptable health and weight were available to conduct the study as designed. This strain was selected because of its general acceptance and suitability for toxicity testing, the availability of historical background data, and a reliable commercial supplier. Upon arrival at the laboratory1, the health status of the mice was determined by a veterinarian and the rats were acclimated to the laboratory environment according to the Standard

Operating Procedures of the Subchronic/Chronic Toxicity section of the Mammalian and Environmental Toxicology Research Laboratory.

During acclimation animals were weighed and randomly assigned to exposure groups using a computer-generated randomization procedure. Animals at the extremes of the body weight distribution were not used in the study. Identification of the animals used for the study was accomplished by inserting a uniquely numbered metal tag in an ear of each animal. One animal had an ear tag which became dislodged during the course of the study; it was replaced with one having the same number and this was noted in the study file. The animal rooms of the testing facility are designed to maintain adequate environmental conditions concerning temperature and humidity and are regulated for the specific species under test. A 12-hour photoperiod was used. Animals were provided Purina Certified Rodent Chow #5002 (Ralston Purina Co., St. Louis, Missouri) and water ad libitum except during exposure. Water and feed analyses were done according to the Standard Operating Procedures of the Mammalian and Environmental Toxicology Research Laboratory.

Inhalation Exposure. Mice were exposed in 1 m3 stainless steel and glass Rochester-type inhalation chambers. Chamber airflow was maintained at approximately 200 liters/minute. Chamber conditions were controlled by a system designed to maintain temperature at approximately 22'C and relative humidity at approximately 50%. The temperature and relative humidity were generally recorded at the end of each exposure period. The test material was vaporized using a modification of the glass J-tube method (Miller et al., 1980). The J-tube was filled with solid test material and 6 mm glass beads. Compressed air was heated with a flame- less heat torch (Model FHT-4, Master Appliance Corportion, Racine, Wisconsin) to the minimum extent necessary to volatilize the test material. The air passing through the J-tube was diluted with the main chamber airstream prior to entering the chamber. The concentration was determined at least three times/exposure period by gas chromatography (Varian 2400, Palo Alto, California) with a flame ionization detector. The gas chromatograph was calibrated with liquid standards prepared in carbon tetrachloride. The GC conditions were as follows: nitrogen flow = 90 ml/minute, hydrogen flow = 47 ml/minute, air flow = 300 ml/minute, detector temperature 265ºC, column temperature = 180ºC, and injector temperature = 268ºC. The material was separated from the solvent with a 6 foot x 1/8 inch stainless steel column packed with 10% SP2100 on 100-120 mesh supelcoport. Measured volumes of chamber air samples were drawn through an impinger containing carbon tetrachloride. The concentration in the trapped sample was determined by interpolation from known standards. The distribution of the vapor inside the chamber was determined prior to animal exposures and the average varied by less than 8% within the chambers.

Observations and Records. All animals were observed after each exposure for exposure-related effects or changes in demeanor. The observations included an evaluation of the fur, eyes, mucous membranes, and respiration. Behavior pattern and nervous system activity were also assessed by specific observation for tremors, convulsions, salivation, lacrimation, and diarrhea, as well as lethargy and other signs of central nervous system depression. An additional daily observation and routine monitoring on weekends was limited to the removal of dead animals and animal husbandry procedures required to ensure the availability of food and water. Animals which died spontaneously during the course of the study were submitted to pathology for examination. Animals found dead outside of the normal working hours or on weekends were refrigerated and examined as soon as possible. All animals were weighed on days 1, 3, 5, 8, and 11 of the study.

Hematology. Blood samples were collected by orbital sinus puncture from mice anesthetized with methoxyflurane immediately prior to necropsy.

The following hematologic parameters were measured for each animal with an Ortho ELT-8 (Ortho Instruments, Boston, Massachusetts): hematocrit (HCT), hemoglobin (HGB), erythrocyte count (RBC), total leukocyte count (WBC), and platelet count (PLAT). Slides for differential leukocyte counts were prepared for all animals. Differential leukocyte counts were performed for all animals from the control and 1.0 ppm exposure groups.

Serum Chemistry. Blood samples for serum analysis were collected at the terminal sacrifice from the posterior orbital sinus. The samples were chilled with crushed ice until centrifuged and then frozen until analyzed. The following parameters were measured with a Centrifichem System (Baker Instruments, Allentown, Pennsylvania): urea nitrogen

(UN), alanine aminotransferase activity (ALT), aspartate aminctrans- ferase activity (AST), alkaline phosphatase activity (AP), glucose (GLUC), total protein (TP), albumin (ALB), globulins (GLOB), cholesterol (CHOL), and triglycerides (TRIG).

Pathology. All surviving animals were sacrificed the day following the last exposure. Each animal was weighed, anesthetized with methoxyflurane and euthanatized. Weights of the brain, heart, liver, kidneys, thymus, and testes were recorded from all animals at the scheduled sacrifice. All animals were examined for gross pathological alterations by a veterinary pathologist. The necropsy included in situ examination of the eyes by a glass-slide technique with fluorescent illumination. A complete set of tissues was collected from each animal and preserved in neutral, phosphate-buffered 10% formalin. The lungs were infused with buffered formalin to their approximate normal inspiratory volume and the nasal cavity was flushed with formalin via the pharyngeal duct to insure rapid fixation of the tissue. A complete histopathologic examination was performed on tissues except auditory sebaceous glands from the control and 1.0 ppm exposure groups. In addition, the liver, kidneys, nasal turbinates, larynx, trachea, and lungs were examined from mice in the 0.1 ppm and 10 ppm groups. Tissues examined histopathologically were processed by conventional techniques, embedded in paraffin, cut to 6 um, stained with hematoxylin and eosin, and evaluated by a veterinary pathologist. Oil-red-O and PAS stains were used in a limited number of animals to aid in defining the liver changes.

Statistical Evaluation. Chamber analytical data, temperature and relative humidity, and white blood cell differential counts were reported with descriptive statistics only (mean and standard deviation). Body weights, absolute and relative organ weights, clinical chemistry data, and appropriate hematology data were evaluated by Bartlett's test for equality of variances. Based on the outcome of Bartlett's test, exploratory data analysis was performed by a parametric or nonparametric analysis of variance (ANOVA), followed by Dunnett's test or Wilcoxon Rank-Sum test with a Bonferroni correction for multiple comparisons. Statistical outliers were identified by a sequential test but were not excluded from analysis. The nominal alpha levels used and references are as follows:

Bartlett's test (Winer, 1971) a = 0.01
Parametric ANOVA (Steel and Torrie, 1973) a = 0.10 Nonparametric ANOVA (Hollander and Wolfe, 1973) a = 0.10
Dunnett's test (Winer, 1971) a = 0.05,
two-sided
Wilcoxon Rank-Sum test a = 0.05, (Hollander and Wolfe, 1973) two-sided Bonferroni correction (Miller, 1966)
Outlier test (Grubbs, 1969) a = 0.02,
two-sided

Because numerous interrelated parameters are statistically compared on the same group of animals, the frequency of false-positive (Type 1) errors may be much greater than the nominal alpha level. Thus, in addition to statistical analyses, the final toxicologic interpretation of the data considers other factors such as dose-response relationships, biological plausibility, and consistency.

1Fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

Result : Exposure Chamber Conditions. The mean daily time-weighted average (TWA) exposure concentrations were very close to the targeted concentrations for the 0.1 and 1.0 ppm groups. The TWA analytical concentration for the 10 ppm target concentration group was 7.32 ppm, which was the maximally attainable chamber concentration in this study.

Chamber humidity and temperature were within acceptable ranges throughout this study.

Antemortem Observations. All male and female mice exposed to 10 ppm died by test day 4. All mice in all other exposure groups survived to study termination. Body weights were decreased on day 3 for both males and females exposed to 10 ppm but no treatment-related changes were seen in any other exposure groups. Most mice exposed to 10 ppm were moribund prior to death. No clinical signs were seen in mice in any other exposure. group.

Pathology Observations. There were no treatment-related changes in hematology, serum chemistry, or organ weight data. The changes seen in RBC, HGB and HCT in female mice exposed to 0.1 ppm were considered to be non-treatment related because of the lack of a concentration-response relationship. All male and female mice exposed to 10 ppm had erosions and/or ulcers in the glandular stomach. Many of these mice also had partially digested blood in the digestive tract, which was considered secondary to the changes in the stomach. The stomach changes were most likely a secondary result of of stress. In addition, all male and female mice exposed to 10 ppm had pale livers. The histopathologic correlate to the grossly pale livers was centrilobular and midzonal necrosis and periportal vacuolation consistent with fatty change in males and centrilobular necrosis and midzonal and periportal vacuolation consistent with fatty change in females. Special stains identified the contents of the vacuoles as lipid in selected animals.

At the highest exposure concentration the liver was the primary target organ. The no-observed-effect level for both male and female mice was 1.0 ppm.

Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
23.09.2004 (4)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : inhalation
Exposure period : 6 h/day
Frequency of treatm. : 5 days/week for 2 weeks
Post exposure period :
Doses : 0.1, 1.0, and 10 ppm
Control group : yes, concurrent vehicle
NOAEL : = 1 - ppm
Method : EPA OPP 82-4

Year	:	1987
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Study Design. Groups of five rats/sex were exposed for 6 hours/day, 5 days/week to target concentrations of 0, 0.1, 1, or 10 ppm for two weeks (nine exposures interrupted by one weekend). On the day following the last exposure, all animals were necropsied. Urine and blood were obtained for selected clinical pathologic evaluations. Major organs were weighed and tissues were saved in neutral, phosphate-buffered 10% formalin for subsequent examination. The highest targeted exposure level, 10 ppm, produced the maximum practically attainable concentration in this study. The lowest exposure level, 0.1 ppm, was chosen to assess a no-observed-effect level. The 1.0 ppm exposure level was chosen to aid in defining a dose response. The study was initiated on May 5, 1986 and rats were necropsied on May 16, 1986.

Test Species and Husbandry. Seven-week old Fischer 344 rats (Charles River Breeding Laboratory, Kingston, New York) were purchased for the study. Extra animals were ordered to ensure that a sufficient number of animals of acceptable health and weight were available to conduct the study as designed. This strain was selected because of its general acceptance and suitability for toxicity testing, the availability of historical background data, and a reliable commercial supplier. Upon arrival at the laboratory1, the health status of the rats was determined by a veterinarian and the rats were acclimated to the laboratory environment according to the Standard Operating Procedures of the Subchronic/Chronic Toxicity section of the Mammalian and Environmental Toxicology Research Laboratory.

During acclimation animals were weighed and randomly assigned to exposure groups using a computer-generated randomization procedure. Animals at the extremes of the body weight distribution were not used in the study. Identification of the animals used for the study was accomplished by inserting a uniquely numbered metal tag in an ear of each animal. The animal rooms of the testing facility are designed to maintain adequate environmental conditions concerning temperature and humidity and are regulated for the specific species under test. A 12-hour photoperiod was used. Animals were provided Purina Certified Rodent Chow #5002 (Ralston Purina Co., St. Louis, Missouri) and water ad libitum except during exposure. Water and feed analyses were done according to the Standard Operating Procedures of the Mammalian and Environmental Toxicology Research Laboratory.

Inhalation Exposure. Rats were exposed in 1 m3 stainless steel and glass Rochester-type inhalation chambers. Chamber airflow was maintained at approximately 200 liters/minute. Chamber conditions were controlled by a system designed to maintain temperature at approximately 22'C and relative humidity at approximately 50%. The temperature and relative humidity were generally recorded at the end of each exposure period. The test material was vaporized using a modification of the glass J-tube method (Miller et al., 1980). The J-tube was filled with solid test material and 6 mm glass beads. Compressed air was heated with a flame- less heat torch (Model FHT-4, Master Appliance Corporation, Racine, Wisconsin) to the minimum extent necessary to volatilize the test material. The air passing through the J-tube was diluted with the main chamber airstream prior to entering the chamber. The concentration was determined at least three times/exposure period by gas chromatography (Varian 2400, Palo Alto, California) with a flame ionization detector. The gas chromatograph was calibrated with liquid standards of Beta 2-Tet prepared in carbon tetrachloride. The GC conditions were as follows: nitrogen flow = 90 ml/minute, hydrogen flow = 47 ml/minute, air flow = 300 ml/minute, detector temperature 265ºC, column temperature = 180ºC, and injector temperature = 265ºC. The material was separated from the solvent with a 6 foot x 1/8 inch stainless steel column packed with 10% SP2100 on 100-120 mesh supelcoport. Measured volumes of chamber air samples were drawn through an impinger containing carbon tetrachloride. The concentration in the trapped sample was determined by interpolation from known standards. The distribution of the vapor inside the chamber was determined prior to animal exposures and the average varied by less than 8% within the chamber.

Observations and Records. All animals were observed after each exposure for exposure-related effects or changes in demeanor. The observations included an evaluation of the fur, eyes, mucous membranes, and respiration. Behavior pattern and nervous system activity were also assessed by specific observation for tremors, convulsions, salivation, lacrimation, and diarrhea, as well as lethargy and other signs of central nervous system depression. An additional daily observation and routine monitoring on weekends was limited to animal husbandry procedures required to ensure the availability of food and water. All animals were weighed on days 1, 3, 5, 8, and 11 of the study.

Hematology. Blood samples were collected by orbital sinus puncture from rats anesthetized with methoxyflurane immediately prior to necropsy. The following hematologic parameters were measured for each animal with an Ortho ELT-8 (Ortho Instruments, Boston, Massachusetts): hematocrit (HCT), hemoglobin (HGB), erythrocyte count (RBC), total leukocyte count (WBC), and platelet count (PLAT). Slides for differential leukocyte counts were prepared for all animals. Differential leukocyte counts were performed for all animals from the control and 10 ppm exposure groups.

Serum Chemistry. Blood samples for serum analysis were collected at the terminal sacrifice from severed cervical blood vessels. The samples were chilled with crushed ice until centrifuged and then frozen until analyzed. The following parameters were measured with a Centrifithem System (Baker Instruments, Allentown, Pennsylvania): urea nitrogen (UN), alanine aminotransferase activity (ALT), aspartate aminotransferase activity (AST), alkaline phosphatase activity (AP), glucose (GLUC), total protein (TP), albumin (ALB), globulins (GLOB), cholesterol (CHOL), and triglycerides (TRIG).

Urinalysis. Urine was collected prior to the 9th exposure. The following parameters were measured using a Urotron test strip analyzer (Biodynamics, Indianapolis, Indiana): bilirubin, glucose, ketones, blood, pH, protein, and urobilinogen. Specific gravity of the urine was measured with a refractometer (American Optical Co., Keene, New Hampshire).

Pathology. All animals were sacrificed the day following the last exposure. The animals were fasted overnight prior to the scheduled sacrifice. Each animal was weighed, anesthetized with methoxyflurane and euthanatized. Weights of the brain, heart, liver, kidneys, thymus, and testes were recorded from all animals at the scheduled sacrifice. All animals were examined for gross pathological alterations by a veterinary pathologist. The necropsy included in situ examination of the eyes by a glass-slide technique with fluorescent illumination. A complete set of tissues was collected from each animal and preserved in neutral, phosphate-buffered 10% formalin. The lungs were infused with buffered formalin to their approximate normal inspiratory volume and the nasal cavity was flushed with formalin via the pharyngeal duct to insure rapid fixation of the tissue. A complete histopathologic examination was performed on tissues except auditory sebaceous glands from the control and 10 ppm exposure groups. In addition, the liver, kidneys, nasal turbinates, larynx, trachea, and lungs were examined from rats in the 0.1 ppm and 1.0 ppm groups. Tissues examined histopathologically were processed by conventional techniques, embedded in paraffin, cut to 6 pm, stained with hematoxylin and eosin, and evaluated by a veterinary pathologist.

Statistical Evaluation. Chamber analytical data, temperature and relative humidity, and white blood cell differential counts were reported with descriptive statistics only (mean and standard deviation). Body weights, absolute and relative organ weights, clinical chemistry data, appropriate hematology data, and urinary specific gravity were evaluated by Bartlett's test for equality of variances. Based on the outcome of Bartlett's test, exploratory data analysis was performed by a parametric or nonparametric analysis of variance (ANOVA), followed by Dunnett's test or Wilcoxon Rank-Sum test with a Bonferroni correction for multiple comparisons. Statistical outliers were identified by a sequential test but were not excluded from analysis. The nominal alpha levels used and references are as follows:

Bartlett's test (Winer, 1971) a = 0.01 Parametric ANOVA (Steel andTorrie, 1973) a = 0.10
Nonparametric ANOVA (Hollander and Wolfe, 1973) a = 0.10
Dunnett's test (Winer, 1971) a = 0.05, two-sided
Wilcoxon Rank-Sum test (Hollander and Wolfe, 1973) a = 0.05, two-sided
Bonferroni correction (Miller, 1966)
Outlier test (Grubbs, 1969) a = 0.02, two-sided

Because numerous interrelated parameters are statistically compared on the same group of animal's, the frequency of false-positive (Type 1) errors may be much greater than the nominal alpha level. Thus, in addition to statistical analyses, the final toxicologic interpretation of the data considers other factors such as dose-response relationships, biological plausibility, and consistency.

1Fully accredited by the American Association-for Accreditation of Laboratory Animal Care (AAALAC).

Result : Exposure Chamber Conditions. The mean daily time-weighted average (TWA) exposure concentrations were very close to the targeted concentrations for the 0.1 and 1.0 ppm groups (Table 2). The TWA analytical concentration for the 10 ppm target concentration group was 7.32 ppm, which was the maximally attainable chamber concentration in this study.

Chamber humidity and temperature were within acceptable ranges throughout this study.

All rats survived to the scheduled sacrifice date. Body weights of male and female rats exposed to 10 ppm were decreased throughout the study though the decreases were not statistically significant. The only clinical observation was the accumulation of reddish material, most likely porphyrin, on the noses of the 10 ppm rats.

There were no changes of toxicologic significance in hematology or urinalysis data from male or female rats at any exposure concentration. Male and female rats exposed to 10 ppm had increases in serum alkaline phosphatase activity, alanine aminotransferase activity, aspartate aminotransferase activl:ty, and decreases in serum cholesterol and triglycerides. Male and female rats exposed to 10 ppm had increased absolute and relative liver weights (statistically significant) and decreased body weights(not statistically significant). Males exposed to 10 ppm also had increases in relative brain, kidney and testes weights and decreased absolute thymus weights. All other changes in clinical pathology parameters were considered spontaneous and not effects of treatment.

Four of five male, and five of five female rats exposed to 10 ppm had enlarged livers at gross necropsy and the females also had pale livers. Histopathologically, this corresponded to midzonal vacuolation consistent with fatty change and periportal hepatocyte individualization in all males. Similar changes consisting of centrilobular and midzonal vacuolation consistent with fatty change and periportal individualization of hepatocytes were evident in all females. All other gross and histopathologic changes were considered spontaneous and not effects of treatment.

The increases in liver weight, gross pathologic changes, serum chemistry effects and histopathologic changes indicate that the liver was the target organ. The effects seen were clearly a result of exposure, but it is important to note that these changes did not result in, nor were the result of hepatocellular necrosis. The decreases in body weight in the 10 ppm were not statistically significant but were probably due to exposure. The organ weight changes in brain, kidney, testes and thymus were most likely a secondary result of the body weight decreases and not a direct effect of treatment since no significant histopathologic effects were observed. The no-observed-effect level for both male and female rats was 1.0 ppm.

Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
23.09.2004 (4)

5.5 GENETIC TOXICITY 'IN VITRO'

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

Type : other: TOPKAT and DEREK QSAR Analysis

Attached document : 2-Chloro-5-trichloromethylpyridine.doc
Chlorinated Pyridines.xls

08.12.2005

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

9. References

(1) Haga, Takahiro; Fujikawa, Kan-ichi; Koyanagi, Tohru; Nakajima, Toshio; Hayashi, Kouji, Heterocycles, CODEN: HTCYAM, 22(1), <1984>, 117-124

(2) MPBPWIN v1.41, © 2000 U.S. EPA

(3) KOWWIN v1.67, © 2000 U.S. EPA

(4) Unpublished data, The Dow Chemical Company.

(5) WSKOWWIN v1.41, © 2004 U.S. EPA

(6) U.S. EPA, 2004. - AOPWin, v1.91, Atmospheric half-life estimating software & experimental value database.

(7) U.S. EPA, 2003. - EPIWin, v3.12; WVOLNT.exe volatilization half-life est. software; & EPI_PHYS.db phys. property database.

(8) U.S. EPA, 2000. - BIOWin, v4.02, Biodegradation probability estimating software.

10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

Chapter : Toxicity
Memo : Comparison of DEREK results from test material and pentachloropyridine.

Remark :

DEREK for Windows report for Pentachloropyridine

Date Created: Monday, December 08, 2003
Version: 7.0.0
Database: N:\Private\Lhasa Ltd\LPS 700\Dfw700.mdb
Database Version: DFW7.0.0_22_09_2003
Testing Against: All Alerts

Species: bacterium
mammal
Salmonella typhimurium
SuperEndpoints: Carcinogenicity
Genotoxicity
Irritation
Miscellaneous endpoints
Respiratory sensitisation
Skin sensitisation
Thyroid toxicity
Consider Tautomers: True
Hydrogen Options: Perceive implicit and explicit hydrogens
Override automatic Log P calculation: False
AutoSave: Off
AutoSave Directory: N:\Private\Lhasa Ltd\LPS 700\work
Name Field:

Compound Name: 2,3,4,5,6-pentachloropyridine

Log Kp: -2.45 Calculated by the Potts & Guy equation
Log P: 2.54 Calculated by the Moriguchi estimation
Molecular Weight: 251.327 Calculated by LPS

Submitted Compound:

List of alerts found:

438 Activated pyridine, quinoline or isoquinoline. Skin sensitisation.
Number of matches = 3

LHASA PREDICTIONS

Skin sensitisation

mammal - Reasoning

Skin sensitisation in mammal is PLAUSIBLE
[Skin sensitisation alert] is [CERTAIN]
[species mammal] is [CERTAIN]

Alert overview: 438 Activated pyridine, quinoline or isoquinoline

Electrophilic substituted pyridines, quinolines or isoquinolines may react with skin protein via a SnAr mechanism. Nucleophilic substitutions proceed slowly at aromatic carbons, but compounds of this type are susceptible to nucleophilic attack at the ring carbon attached to R1 in the presence of electron withdrawing groups in the ortho and para ring positions. The ring nitrogens can exert a strong activation, and may behave analogously to nitro groups on activated benzenes (alert 415). The activation is enhanced further if the ring nitrogen is positively charged as N-oxide or N-Me. The reactivity of these compounds is dependent on the combination of the strength of the leaving group R1, and the strength and number of the electron withdrawing groups R2 [Roberts, March, Landsteiner and Jacobs, De Boer and Dirkx].

The presence of a skin sensitisation structural alert within a molecule indicates the molecule has the potential to cause skin sensitisation. Whether or not the molecule will be a skin sensitiser will also depend upon its percutaneous absorption. Generally, small lipophilic molecules are more readily absorbed into the skin and are therefore more likely to cause sensitisation.

References:

Title: Studies on the sensitization of animals with simple chemical compounds. II.
Author: Landsteiner K and Jacobs J.
Source: Journal of Experimental Medicine, 1936, 64, 625-639.

Title: Annex to commission directive 93/72/EEC of 1 September 1993 adapting to technical progress for the nineteenth time council directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, ...
Author: Commission of the European Communities.
Source: Official Journal of the European Communities, 1993, 36 (L258A), 1-1409.

Title: Linear free energy relationships for reactions of electrophilic halo- and pseudohalobenzenes, and their application in prediction of skin sensitization potential for SnAr electrophiles.
Author: Roberts DW.
Source: Chemical Research in Toxicology, 1995, 8, 545-551.

Title: Aromatic nucleophilic substitution.
Author: March J.
Source: Advanced organic chemistry. Reactions, mechanisms, and structure, 3rd edition, March J, Wiley-Interscience, New York, 1985, 576-607.

Title: Activating effects of the nitro group in aromatic substitutions.
Author: De Boer TJ and Dirkx IP.
Source: The Chemistry of the nitro and nitroso groups. Part 1,

Chapter 8, Feuer H (editor), Interscience Publishers, New York, 1969, 487-612.

Locations:

Examples: (438 Activated pyridine, quinoline or isoquinoline)

Example 1. 2-fluoro-5-trifluoromethylpyridine
CAS Number: 69045-82-5

Test Data: (2-fluoro-5-trifluoromethylpyridine)

1.
Species: unspecified
Assay: unspecified
Result: R43

References:

Title: Annex to commission directive 93/72/EEC of 1 September 1993 adapting to technical progress for the nineteenth time council directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, ...
Author: Commission of the European Communities.
Source: Official Journal of the European Communities, 1993, 36 (L258A), 1-1409.

Example 2. 2,3,5,6-tetrachloro-4-(methylsulphonyl)pyridine
CAS Number: 13108-52-6

Test Data: (2,3,5,6-tetrachloro-4-(methylsulphonyl)pyridine)

1.
Species: unspecified
Assay: unspecified
Result: R43

References:

Title: Commission directive 94/69/EC of 19 December 1994 adapting to technical progress for the twenty-first time council directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging ...
Author: Commission of the European Communities.
Source: Official Journal of the European Communities, 1994, 37 (L381), 1-1485.

DEREK for Windows report for 2-Chloro-5-trichloromethylpyridine

Date Created: Monday, December 08, 2003
Version: 7.0.0
Database: N:\Private\Lhasa Ltd\LPS 700\Dfw700.mdb
Database Version: DFW7.0.0_22_09_2003
Testing Against: All Alerts

Species: bacterium
mammal
Salmonella typhimurium
SuperEndpoints: Carcinogenicity
Genotoxicity
Irritation
Miscellaneous endpoints
Respiratory sensitisation
Skin sensitisation
Thyroid toxicity
Consider Tautomers: True
Hydrogen Options: Perceive implicit and explicit hydrogens
Override automatic Log P calculation: False
AutoSave: Off
AutoSave Directory: N:\Private\Lhasa Ltd\LPS 700\work
Name Field:

Compound Name: 2-Chloro-5-trichloromethylpyridine

Log Kp: -2.325 Calculated by the Potts & Guy equation
Log P: 2.54 Calculated by the Moriguchi estimation
Molecular Weight: 230.909 Calculated by LPS

Submitted Compound:

List of alerts found:

122 Di- to poly-halogenated alkane or cycloalkane. Carcinogenicity. Number of matches = 1
346 Trichloromethyl aromatic compound. Mutagenicity. Number of matches = 1

LHASA PREDICTIONS

Carcinogenicity

mammal - Reasoning

Carcinogenicity in mammal is PLAUSIBLE
[Carcinogenicity alert set 1] is [CERTAIN]
[Species dependent variable 22] is [PLAUSIBLE]
[alert 122] is [CERTAIN]
[species mammal] is [CERTAIN]

Alert overview: 122 Di- to poly-halogenated alkane or cycloalkane

Some halo-alkanes are alkylating agents, not needing metabolic activation.

However, free-radical pathways have been postulated for 1,1,1-trihaloalkanes.

References:

Title: General principles for evaluating the safety of compounds used in food-producing animals.
Author: Food and Drug Administration (FDA).
Source: Food and Drug Administration Report, 1986, III-7-III-17, July 1994 revision available at "http://www.fda.gov/cvm/guidance/guideline3toc.html".

Locations:

Examples: (122 Di- to poly-halogenated alkane or cycloalkane)

(No examples)

Custom Examples: (122 Di- to poly-halogenated alkane or cycloalkane)

(No examples)

Mutagenicity

bacterium - Reasoning

Mutagenicity in vitro in bacterium is PLAUSIBLE
[alert 346] is [CERTAIN]
[species bacterium] is [CERTAIN]

Salmonella typhimurium - Reasoning

Mutagenicity in vitro in Salmonella typhimurium is PLAUSIBLE
[alert 346] is [CERTAIN]
[species bacterium] is [CERTAIN]

Alert overview: 346 Trichloromethyl aromatic compound

Mutagenicity: Ames test

This alert describes the mutagenicity of trichloromethyl aromatic compounds.

Compounds of this type generally exhibit mutagenicity in the Ames test, notably in Salmonella strains TA98 and TA100 in the presence, but not absence, of S9 [Zeiger et al 1988, 1992, Yasuo et al]. Trifluoromethyl aromatic compounds are not, however, mutagenic in the Ames test [Zeiger et al 1988, 1992, Haworth et al].

References:

Title: Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals.
Author: Zeiger E, Anderson B, Haworth S, Lawlor T and Mortelmans K.
Source: Environmental and Molecular Mutagenesis, 1992, 19

(supplement 21), 2-141.

Title: Salmonella mutagenicity test results for 250 chemicals.
Author: Haworth S, Lawlor T, Mortelmans K, Speck W and Zeiger E.
Source: Environmental Mutagenesis, 1983, 5 (supplement 1), 3-142.

Title: Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals.
Author: Zeiger E, Anderson B, Haworth S, Lawlor T and Mortelmans K.
Source: Environmental and Molecular Mutagenesis, 1988, 11 (supplement 12), 1-158.

Title: Mutagenicity of benzotrichloride and related compounds.
Author: Yasuo K, Fujimoto S, Katoh M, Kikuchi Y and Kada T.
Source: Mutation Research, 1978, 58, 143-150.

Locations:

Examples: (346 Trichloromethyl aromatic compound)

(No examples)

Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
23.09.2004

10.3 RISK ASSESSMENT

RECEIVED
OPPT CBIC

05 DEC 27 AM 9:48

I U C L I D

Data Set

Existing Chemical	: ID: 1817-13-6
CAS No.	: 1817-13-6
Generic name	: 3,6-Dichloro-2-trichloromethylpyridine

Producer related part	
Company	: Dow Chemical, TERC
Creation date	: 15.07.2004
Substance related part	
Company	: Dow Chemical, TERC
Creation date	: 15.07.2004
Status	:
Memo	:
Printing date	: 08.12.2005
Revision date	:
Date of last update	: 08.12.2005
Number of pages	: 34
Chapter (profile)	: Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	: Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	: Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	manufacturer
Name	:	The Dow Chemical Company
Contact person	:	
Date	:	
Street	:	2020 Dow Center
Town	:	48674 Midland, Michigan
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

Reliability : (1) valid without restriction
16.07.2004

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

16.07.2004

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

3,6-Penta

Reliability : (1) valid without restriction
16.07.2004

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= 47 - 48 °C
Sublimation	:	
Method	:	other
Year	:	1963
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Study conducted prior the advent of GLP.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

20.09.2004 (1)

2.2 BOILING POINT

Value	:	= 272 °C at
Decomposition	:	
Method	:	other
Year	:	2003
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Calculated value using EPA's programs.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

20.09.2004 (2)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	at 25 °C
Decomposition	:	
Method	:	other (calculated)
Year	:	2003
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Calculated value using EPA's programs.
Result	:	Calculated value = 0.0052 mm Hg @ 25 degrees C.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

20.09.2004 (2)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	= 4 at 25 °C

pH value :
Method : other (calculated)
Year : 2003
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Value calculated using EPA's programs.
Source : The Dow Chemical Company, Midland, MI.
20.09.2004 (3)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 7.5 mg/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other
Year : 2003
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Value calculated using EPA's programs.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
08.12.2005 (4)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

Method : other
Year : 2003
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Not Applicable. Not expected to have significant oxidizing or reducing potential.

Source : The Dow Chemical Company, Midland, MI.
20.09.2004

2.12 DISSOCIATION CONSTANT

Method : other
Year : 2003
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Not applicable. Does not ionize within environmentally relevant pH ranges.
Source : The Dow Chemical Company, Midland, MI.
20.09.2004

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

INDIRECT PHOTOLYSIS

Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	= .0000000000000139 cm^3/(molecule*sec)
Degradation	:	= 50 % after 768 day(s)
Deg. product	:	
Method	:	other (calculated)
Year	:	2004
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Values calculated using EPA's programs.
Result	:	The rate constant for the vapor phase reaction with photochemically produced hydroxyl radicals is estimated to be 0.0139E-12 cm3/molecule-sec at 25C; which corresponds to a tropospheric half-life of 768.141 days, (12-hr day; 1.5E+06 OH/cm3).
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

20.09.2004 (5)

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	
Air	:	32.9 % (Fugacity Model Level I)
Water	:	6.7 % (Fugacity Model Level I)
Soil	:	59.1 % (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	81.9 % (Fugacity Model Level II/III)
Method	:	other
Year	:	2005
Remark	:	Values calculated using EPA's programs.
Source	:	The Dow Chemical Company, Midland, MI.
Attached document	:	36DC2TCMFugacity.doc
Reliability	:	(2) valid with restrictions

08.12.2005 (6) (7)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Deg. product :
Method : other
Year : 2004
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Values calculated using EPA's programs.
Result : Material is estimated not to biodegrade fast using a linear and non-linear SAR method, and not to be readily biodegradable using a MITI linear and non-linear SAR method. Ultimate and primary biodegradation is estimated to occur in 2.66 weeks-months.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
20.09.2004 (8)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

BCF : = 238.4
Elimination :
Method : other
Year : 2004
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Value calculated using EPA's programs.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
20.09.2004 (9)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 1000 - 2000 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	male
Number of animals	:	15
Vehicle	:	other: corn oil
Doses	:	130, 250, 500, 1000, 2000 mg/kg bw
Method	:	other
Year	:	1982
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Young adult male rats were fasted overnight. They were administered the material as a suspension in corn oil at a dose volume of 4 ml/kg bw at dose levels of 130, 250, 500, 1000, or 2000 mg/kg bw. Animals were observed closely for two weeks, then submitted for pathological examination. All animals which died prior to scheduled necropsy were also submitted for pathological examination. Body weights were recorded on the day of treatment (Study Day 0), and Study Days 1, 8, and 15.
Remark	:	GLP not compulsory at time study was performed.
Result	:	All rats given 2000 mg/kg died within 3 days of treatment. All other rats survived until study termination. Clinical signs observed in rats given 1000 or 2000 mg/kg included lethargy, prostration, palpebral closure, rapid/shallow breathing, occasional body tremors, and loss of motor coordination. No treatment-related changes were observed during gross pathological examination. The oral LD50 was between 1000 and 2000 mg/kg.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(2) valid with restrictions Study conducted in accordance with generally accepted scientific principles.

06.08.2004 (10)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	.5 g
Exposure	:	Semiocclusive
Exposure time	:	24 hour(s)
Number of animals	:	2

Vehicle	:	water
PDII	:	
Result	:	irritating
Classification	:	
Method	:	other
Year	:	1982
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : A male rabbit was prepared by shaving the hair from the entire abdomen with a straight razor and barber soap. The animal was then rested for several days to allow any abrasions to heal completely and to be sure skin was suitable for use. Two sites on the abdomen were used for applications: one intact, the other cross-hatched with a sharp hypodermic needle to penetrate the stratum corneum but not to produce more than a trace of bleeding. Ten applications were made to the intact abdominal site over a period of 14 days. Three consecutive daily applications were made to the abraded site. Both abdominal sites were covered with 1X1 cotton pads and held place with a single cotton cloth taped to remaining body hair. Applications were discontinued upon production of a substantial skin burn, or if the animal died. A second male rabbit was treated in a similar manner, except that the test material was moistened with water during the applications.

Remark : GLP not compulsory at time study was performed.

Result : Prolonged and repeated (10 applications) contact with the undiluted test material under both dry and moist conditions resulted moderate (dry) to marked (moist) redness, slight swelling, moderate exfoliation, and superficial burns. Results indicate that systemic injury will not occur at concentrations which do not produce skin injury.

Source : The Dow Chemical Company, Midland, MI.

Reliability : (2) valid with restrictions
Study conducted in accordance with generally accepted scientific principles.

06.08.2004 (10)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	.1 g
Dose	:	
Exposure time	:	1 hour(s)
Comment	:	
Number of animals	:	1
Vehicle	:	none
Result	:	slightly irritating
Classification	:	
Method	:	other
Year	:	1982
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Both eyes of a female New Zealand White rabbit were stained with 5% fluorescein dye and examined for evidence of injury or alterations. The rabbit was then allowed to rest for 24 hours before test.

0.1 g of the material were introduced into the right eye. The eye was washed within 30 seconds for 2 minutes in a flowing stream of tepid water. 0.1 g of material were introduced in a similar fashion to the left eye, but this eye was left unwashed.

Immmediately after instillation into each eye, the rabbit was examined for signs of discomfort. Within 2-3 minutes after the unwashed eye was treated, each eye was observed for conjunctival and corneal response. Similar observations were made on both eyes at 1 hour, 24 hours, 48 hours, and 6-8 days post-treatment. Examinations were conducted both with and without fluorescein dye.

Remark : GLP not compulsory at time study was performed.

Result : Instillation of the test material into the rabbit eye resulted in slight discomfort, moderate conjunctival redness and swelling, moderate reddening of the iris and transient corneal injury. All signs of irritation were essentially absent 48 hours after treatment.

Source : The Dow Chemical Company, Midland, MI.

Reliability : (2) valid with restrictions
Study conducted in accordance with generally accepted scientific principles.

06.08.2004 (10)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : inhalation
Exposure period : 6 h/day
Frequency of treatm. : 5 days/week for 9 exposures
Post exposure period :
Doses : 0.05, 0.32, 1.35 ppm
Control group : yes, concurrent vehicle
NOAEL : = .32 ppm
LOAEL : = 1.35 ppm
Method : EPA OPPTS 870.3465
Year : 1990
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Study Design. Groups of 5 rats/sex and 5 mice/sex were exposed to 0, 0.05, 0.32 or 1.35 ppm (0, 0.5, 3.5 and 14.6 micrograms/liter, respectively) 3,6-Penta for 6 hours/day, 5 days/week for 9 exposures. The highest concentration was the maximum practically attainable concentration. Whole body exposures were conducted under dynamic airflow conditions. Animals were observed daily and weighed at selected intervals. Urine was collected from rats and evaluated immediately prior to the last exposure. All animals were necropsied on the day following the last exposure. Blood samples were obtained for hematologic and clinical chemistry determinations. Major organs were weighed and tissues were evaluated histopathologically.

Test Material. A sample of 3,6-dichloro-2-trichloromethylpyridine (lot # GW5-88p5) was obtained from Western Division of The Dow Chemical Company. The material was reported by Western Division to be 98% pure and was found to be 97.9% pure (Hummel, 1988) based on gas chromatographic analysis.

Test Species and Husbandry. Male and female Fischer 344 (F-344) rats, 6 weeks of age, were obtained from Charles River Breeding Laboratories, Inc., Kingston, NY. Selection of this species was based on a variety of considerations including hardiness, low incidence of respiratory disease and historical control data. Upon arrival at the laboratory,1 the health status of the animals was determined by the laboratory veterinarian.

The rats were acclimated to the laboratory for approximately two weeks prior to exposure to the test material. Animals were weighed, randomized by body weight into groups of five and individually identified with an alphanumeric ear tag. Animals were placed in rooms designed to maintain adequate environmental conditions concerning temperature, relative humidity and photocycle for the specific species under test. Water and Purina Certified Rodent Chow #5002 (Ralston Purina Co., St. Louis, MO) were available ad libitum for all animals except during exposure. Analysis of Purina Certified Rodent Chow was supplied by the Ralston Purina Company to confirm that the diet provided adequate nutrition and to quantify the levels of selected contaminants associated with the formulation process.

Analysis of tap water (municipal water supply) was performed in accordance with Laboratory Standard Operating Procedures.

Exposure Chambers. Whole-body exposure to vapors of the test material was conducted in 157 liter stainless steel and glass exposure chambers (50 cm wide x 50 cm high x 50 cm deep with a pyramidal top and bottom) under dynamic airflow conditions. Chamber airflow was maintained at approximately 30 liters/minute.

Generating System. Vapors of 3,6-Penta were generated using a modification of the glass J-tube method (Miller et al., 1980). The J-tube was packed with glass beads and test material. Compressed air, preheated with a flameless torch (FHT-4, Master Appliance, Racine, WI) to the minimum extent necessary (maximum temperature = 40°C), passed through the J-tube to facilitate vaporization of the solid test material. Although the test material was 97.9% pure, the impurities in the test material were much more volatile. In preliminary work prior to animal exposures, a freshly packed J-tube was prepared and chamber air samples were trapped with an impinger containing toluene. The chamber air contained six chlorinated pyridines (Putzig, 1988). The test material, 3,6-Penta, accounted for 43% (area percent) of the chlorinated pyridines collected in the toluene trap; 2, 3, 5, 6-tetrachloropyridine and 2, 3-dichloro-6-trichloromethylpyridine accounted for 28 and 18%, respectively. The remaining three chlorinated pyridines, 2, 3, 4, 6-tetrachloropyridine, 2, 3, 4, 5, 6-pentachloropyridine, and 2, 3, 4-trichloro-6-trichloromethylpyridine accounted for 10% of the total material. A chamber air sample collected after purging the same J-tube with air for 25 hours contained 63% 3,6-Penta and 22% 2, 3-dichloro-6-trichloromethylpyridine. Animals were subsequently exposed to test material that had been purged with compressed air for at least 27 hours. Hence this study did not include an assessment of the toxicological properties of the more volatile components of the test material which were purged prior to conducting animal exposures.

Chamber Monitoring. Airflow through each chamber was determined with a manometer. The manometer was calibrated with a DTM-115 gas meter (Singer Aluminum Diaphragm Meter, American Meter Division, Philadelphia, PA) prior to the start of the study. The temperature and relative humidity in the chamber were controlled by a system designed to maintain temperature and relative humidity at approximately 22°C and 50%, respectively. Chamber airflow, temperature (minimum and maximum) arid relative humidity were recorded at the end of each 6-hour exposure period.

The nominal concentration of the test material in each chamber was. calculated as accurately as possible based on the amount of test material used and the airflow through the chamber for each exposure period. However, the nominal concentration was of limited utility due to the small amount of test material used each day and the relative insensitivity of the balance necessary to weigh the heavy J-tubes (limit of detection for nominal concentration was 0.9 ppm).

The analytical concentration of 3,6-Penta in the chamber was determined at least 3 times/exposure period by gas chromatography (HP-5890A, Hewlett Packard, Avondale, PA) using a flame ionization detector. The gas chromatographic conditions were as follows: helium flow = 30 ml/min, hydrogen flow = 30 ml/min, air flow = 300 mI/mm, injector temperature = 200°C, column temperature = 160°C and detector temperature = 250°C. A 5 meter x 0.53 mm HP-i methyl silicone capillary column was used for separation of the test material from toluene. The gas chromatograph was calibrated with liquid standards of 3,6-Penta dissolved in toluene. Measured volumes of chamber air were drawn through an impinger containing toluene and the concentration interpolated from known standards. The analytical system was checked prior to each exposure with at least one standard of known concentration.

Prior to animal exposures the distribution of test material was determined from 4 sample points at the extremes of the animal breathing zone and the reference point within the chamber. The reference point was approximately 15 an from the breathing zone. The concentration of test material within the 4 sample locations for each chamber ranged from 77-139% from the mean reference mean value. Because of the relatively large range noted during the distribution check, each group of male and female rats was rotated daily within the chamber.

Chamber Concentration. Groups of 5 rats/sex were exposed to analytically measured concentrations of 0, 0.05, 0.32 and 1.35 ppm (0.0, 0.5, 3.5 and 14.6 micrograms/liter, respectively) 3,6-Penta for 6 hours/day, 5 days/week for 9 exposures (exposures occurred on test days 1-5 and 8-11). The highest concentration was the maximum practically attainable concentration. These exposure levels, 0.05, 0.32 and 1.35 ppm, corresponded to target concentrations of 0, 0.1, 0.5 and 1.5 ppm 3,6-Penta. At the same time, these animals were also exposed to an impurity in the test material at concentrations as high as 0.01, 0.07 and 0.3 ppm 2,3~dichloro-6-trichloromethylpyridine.

Observations and Records. Each animal was examined ophthalmologically with a pen light prior to the initial exposure to 3,6-Penta; there were no significant ocular abnormalities noted. All animals were observed daily after exposure for overt signs of toxicity or changes in demeanor. These observations included an evaluation of the fur, eyes, mucous membranes and respiration. Behavior pattern and nervous system activity were assessed by specific observations for lethargy, tremors, convulsions, salivation, lacrimation, diarrhea and other signs of altered central nervous system function. An additional daily observation and routine monitoring on weekends were limited to animal husbandry procedures required to ensure the availability of food and water. All animals were weighed on test days 1, 3, 5,8, and 11.

Clinical Laboratory Determinations

Hematology. Blood samples were collected by orbital sinus puncture from rats anesthetized with methoxyflurane immediately prior to necropsy. The following hematologic parameters were evaluated for each animal with an Ortho ELT-8 (Ortho Instruments, Boston, MA): hematocrit (HCT), hemoglobin (HGB), erythrocyte count (RBC), total leukocyte (WBC) and platelet (PLAT) count. Slides for differential leukocyte counts were prepared for all animals. The differential count consisted of counting 100 leukocytes per animal on a Wright's stained blood smear. In addition, the morphology of the leukocytes, erythrocytes and platelets was assessed during the differential count.

Clinical Chemistry. Blood samples for serum analyses were collected at the terminal sacrifice from the orbital sinus of rats. Serum samples were chilled with crushed ice or refrigerated until analyzed. The following parameters were measured with a CentrifiChem automated chemistry analyzer (Baker Instruments Corp., Allentown, PA): urea nitrogen (UN), alanine aminotransferase activity (ALT), aspartate aminotransferase activity (AST), alkaline phosphatase activity (AP), glucose (GLUC), total protein (TP), albumin (ALE), globulin (GLOB), cholesterol (CHOL) and triglycerides (TRIG).

Urinalyses. Urine was collected from rats immediately prior to the last exposure. Each specimen was evaluated for color and appearance. The following parameters were measured using a Urotron test strip analyzer (Biodynamics, Indianapolis, IN): bilirubin, glucose, ketones, blood, pH, protein and urobilinogen. Specific gravity of the urine was measured with a refractometer (American Optical Company, Keene, NH). Microscopic examination of the sediments of pooled samples by exposure group was performed.

Pathology. All animals were necropsied the day following the last exposure to the test material. All rats were fasted overnight prior to the scheduled necropsy. Each animal was weighed, anesthetized with methoxyflurane and humanely euthanized. Weights of the brain, heart, liver, kidneys and testes were recorded from all animals at the scheduled sacrifice. All animals were examined for gross pathological alterations by a veterinary pathologist. The necropsy included in situ examination of the eyes using a moistened glass-slide pressed against the corneal surface. A complete set of tissues was collected from each animal and preserved in neutral, phosphate-buffered 10% formalin. The lungs were infused with buffered formalin to their approximate normal inspiratory volume and the nasal cavities were flushed with formalin via the pharyngeal duct to insure rapid fixation.

A complete histopathologic examination of tissues was made from all animals in the control and highest exposure group. In addition, the livers from rats exposed to lower concentrations of test material were examined microscopically. Tissues were processed by conventional techniques, sectioned at approximately 6 microns, stained with hematoxylin and eosin and evaluated with light microscopy by a veterinary pathologist.

Statistical Evaluation. Descriptive statistics (mean and standard deviation) was used to report chamber concentrations, temperature and relative humidity and white blood cell differential counts.

All remaining parameters examined statistically were first tested for equality of variance using Bartlett's test. Since the equality of variance was not rejected in any parameter examined, each parameter was subjected to appropriate parametric analysis as described below. In-life body weight was evaluated using a three-way analysis of variance (ANOVA) with the factors of sex, dose and time interval (Winer, 1971). Hematology (excluding differential WBC) and clinical chemistry parameters, terminal body weight, organ weight (absolute and relative except testes) and urine specific gravity were evaluated using a two-way ANOVA with the factors of sex and dose (Winer, 1971). Results for absolute and relative testes weights were analyzed using a one way ANOVA. If significant dose effects were determined in the one-way ANOVA, then separate doses were compared to controls using Dunnett's test.

For those parameters examined by a two-way ANOVA, examination was made first for a significant sex-dose interaction, If this existed, a one-way ANOVA was done separately for each sex. If no sex-dose interaction was identified, and a dose effect was identified, or if in the subsequent ANOVA's separated by sex a dose effect was identified, then separate ANOVA's were used for each exposure group with control. To control for multiple comparisons with control, a Bonferroni correction was used.

The nominal alpha levels used and test references included:
One-Way ANOVA
Bartlett's test (Winer, 1971) a = 0.01
ANOVA (Steel and Torrie, 1960) a = 0.10
Dunnett's test (Winer, 1971) a = 0.05, two-sided

Two-Way ANOVA
Bartlett's test (Winer, 1971) a = 0.01
First ANOVA (Winer, 1971)
Sex-dose a = 0.05
Dose factor a=0.10
Second ANOVA (Winer, 1971)
Sex-dose a = 0.05
Dose factor a = 0.05

Three-Way ANOVA
Bartlett's test (Winer, 1971) a = 0.01
First ANOVA (Winer, 1971)
Time-sex-dose a = 0.01
Sex-dose a = 0.05
Sex-time a = 0.05
Time-dose a = 0.05
Dose a = 0.10

Second ANOVA (Winer, 1971)
Time-sex-dose a = 0.01
Sex-dose a = 0.05
Sex-time a = 0.05
Time-dose a = 0.05
Dose a = 0.05

Because numerous measurements are statistically compared in the same group of animals, the overall false positive rate (Type I errors) could be much greater than the above cited alpha levels might suggest. As a consequence, the final interpretation of numerical data considered statistical analyses along with other factors, such as dose-response relationships and whether the results were plausible in light of other biological and pathological findings.

1 Accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

Result : Animals were exposed to time-weighted average concentrations (TWA) of 0.05, 0.32 or 1.35 ppm of 3,6-Penta for 6 hours/day, 5 days/week for 9 exposures (Table 3). These concentrations corresponded to target concentrations of 0, 0.1, 0.5 and 1.5 ppm 3,6-Penta. The highest concentration, 1.35 ppm 3,6-Penta, was the maximum practically attainable concentration without aerosol formation in the chamber. The nominal concentration was approximately four times higher than the analytical concentration for each exposure level. As previously mentioned, the nominal concentration was calculated as accurately as possible. However, the lower calculation limit for nominal concentrations was 0.9 ppm due to the small amount of test material used each day and the heavy generation apparatus (4000 grams in weight) which required a balance with limited sensitivity (0.1 grams sensitivity). Temperature and relative humidity values for animals exposed to the various concentrations of 3,6-Penta were comparable to control values during the 2 week study.

RATS. All animals survived the 9 exposures to concentrations as high as 1.35 ppm 3,6-Penta with no overt signs of toxicity or changes in demeanor observed. Body weights of male and female rats exposed to 3,6-Penta were comparable to control values.

Hematology values for male and female rats exposed to 3,6-Penta were comparable to control values. Specific gravity of the urine from male rats exposed to 1.35 ppm 3,6-Penta was statistically significantly decreased from control animals. Although not statistically significant, the mean urinary specific gravity in females exposed to 0.32 and 1.35 ppm was also substantially lower than for control rats. However, these urine specific gravity values of animals exposed to 3,6-Penta were within the range of normal historical control group values (range for male rats 1.033-1.069, range for female rats 1.017-1.059) and thus were not considered to be exposure-related. All other urinary parameters measured were comparable to control values. Alkaline phosphatase activity was slightly but statistically significantly increased in female rats exposed to 1.35 ppm 3,6-Penta but was still within the range of historical control values (range 74-222mU/ml) for female rats used in two-week inhalation studies. Moreover, the mean alkaline phosphatase activity value for male rats exposed to 1.35 ppm was comparable to control values. All remaining clinical chemistry values for male and female rats exposed to 3,6-Penta were comparable to control values.

Absolute and relative liver weights for male and female rats exposed to 1.35 ppm 3,6-Penta were statistically significantly increased (absolute liver weights were increased 9.4 and 14.0%, respectively) from control values. All remaining absolute and relative organ weight values for rats exposed to 3,6-Penta were comparable to control values.

There were no exposure-related gross pathologic or histopathologic observations in rats. Except for the liver, microscopic observations in other tissues were infrequent and all were considered incidental and/or spontaneous events. Although a statistically significant increase in alkaline phosphatase activity in female rats and absolute and relative liver weights of male and female rats exposed to 1.35 ppm was observed, this was not accompanied by exposure-related gross or microscopic changes in the liver. However, some male rats from each exposure group and one female control rat had focal or multifocal areas of necrosis with inflammation usually beneath the capsule in one liver lobe. These lesions were probably due to trauma to the liver during animal handling procedures.

Source : The Dow Chemical Company, Midland, MI.
Conclusion : The No-Observed-Effect-Level (NOEL) in this study was considered to be 0.32 ppm 3,6-Penta.
Reliability : (1) valid without restriction
20.09.2004 (11)

Type : Sub-chronic
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : inhalation
Exposure period : 6 h/day
Frequency of treatm. : 5 days/week for 9 exposures
Post exposure period :
Doses : 0.05, 0.32, 1.35 ppm
Control group : yes, concurrent vehicle

NOAEL	:	= .32 - ppm
Method	:	EPA OPPTS 870.3465
Year	:	1990
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Study Design. Groups of 5 mice/sex were exposed to 0, 0.05, 0.32 or 1.35 ppm (0, 0.5, 3.5 and 14.6 micrograms/liter, respectively) 3,6-Penta for 6 hours/day, 5 days/week for 9 exposures. The highest concentration was the maximum practically attainable concentration. Whole body exposures were conducted under dynamic airflow conditions. Animals were observed daily and weighed at selected intervals. Urine was collected from rats and evaluated immediately prior to the last exposure. All animals were necropsied on the day following the last exposure. Blood samples were obtained for hematologic and clinical chemistry determinations. Major organs were weighed and tissues were evaluated histopathologically.

Test Material. A sample of 3,6-dichloro-2-trichloromethylpyridine (lot # GW5-88p5) was obtained from Western Division of The Dow Chemical Company. The material was reported by Western Division to be 98% pure and was found to be 97.9% pure (Hummel, 1988) based on gas chromatographic analysis.

Test Species and Husbandry. Male and female B6C3F1 mice, 6 weeks of age, were obtained from Charles River Breeding Laboratories, Inc., Raleigh, NC. Selection of this species was based on a variety of considerations including hardiness, low incidence of respiratory disease and historical control data. Upon arrival at the laboratory,1 the health status of the animals was determined by the laboratory veterinarian.

The mice were acclimated to the laboratory for approximately two weeks prior to exposure to the test material. Animals were weighed, randomized by body weight into groups of five and individually identified with an alphanumeric ear tag. Animals were placed in rooms designed to maintain adequate environmental conditions concerning temperature, relative humidity and photocycle for the specific species under test. Water and Purina Certified Rodent Chow #5002 (Ralston Purina Co., St. Louis, MO) were available ad libitum for all animals except during exposure. Analysis of Purina Certified Rodent Chow was supplied by the Ralston Purina Company to confirm that the diet provided adequate nutrition and to quantify the levels of selected contaminants associated with the formulation process.

Analysis of tap water (municipal water supply) was performed in accordance with Laboratory Standard Operating Procedures.

Exposure Chambers. Whole-body exposure to vapors of the test material was conducted in 157 liter stainless steel and glass exposure chambers (50 cm wide x 50 cm high x 50 cm deep with a pyramidal top and bottom) under dynamic airflow conditions. Chamber airflow was maintained at approximately 30 liters/minute.

Generating System. Vapors of 3,6-Penta were generated using a modification of the glass J-tube method (Miller et al., 1980). The J-tube was packed with glass beads and test material. Compressed air, preheated with a flameless torch (FHT-4, Master Appliance, Racine, WI) to the minimum extent necessary (maximum temperature = 40°C), passed through the J-tube to facilitate vaporization of the solid test material. Although the test material was 97.9% pure, the impurities in the test material were much more volatile. In preliminary work prior to animal exposures, a freshly packed J-tube was prepared and chamber air samples were trapped with an impinger containing toluene. The chamber air contained six chlorinated pyridines (Putzig, 1988). The test material, 3,6-Penta, accounted for 43% (area percent) of the chlorinated pyridines collected in the toluene trap; 2, 3, 5, 6-tetrachloropyridine and 2, 3-dichloro-6-trichloromethylpyridine accounted for 28 and 18%, respectively. The remaining three chlorinated pyridines, 2, 3, 4, 6-tetrachloropyridine, 2, 3, 4, 5, 6-pentachloropyridine, and 2, 3, 4-trichloro-6-trichloromethylpyridine accounted for 10% of the total material. A chamber air sample collected after purging the same J-tube with air for 25 hours contained 63% 3,6-Penta and 22% 2, 3-dichloro-6-trichloromethylpyridine. Animals were subsequently exposed to test material that had been purged with compressed air for at least 27 hours. Hence this study did not include an assessment of the toxicological properties of the more volatile components of the test material which were purged prior to conducting animal exposures.

Chamber Monitoring. Airflow through each chamber was determined with a manometer. The manometer was calibrated with a DTM-115 gas meter (Singer Aluminum Diaphragm Meter, American Meter Division, Philadelphia, PA) prior to the start of the study. The temperature and relative humidity in the chamber were controlled by a system designed to maintain temperature and relative humidity at approximately 22°C and 50%, respectively. Chamber airflow, temperature (minimum and maximum) arid relative humidity were recorded at the end of each 6-hour exposure period.

The nominal concentration of the test material in each chamber was. calculated as accurately as possible based on the amount of test material used and the airflow through the chamber for each exposure period. However, the nominal concentration was of limited utility due to the small amount of test material used each day and the relative insensitivity of the balance necessary to weigh the heavy J-tubes (limit of detection for nominal concentration was 0.9 ppm).

The analytical concentration of 3,6-Penta in the chamber was determined at least 3 times/exposure period by gas chromatography (HP-5890A, Hewlett Packard, Avondale, PA) using a flame ionization detector. The gas chromatographic conditions were as follows: helium flow = 30 ml/min, hydrogen flow = 30 ml/min, air flow = 300 mI/mm, injector temperature = 200°C, column temperature = 160°C and detector temperature = 250°C. A 5 meter x 0.53 mm HP-i methyl silicone capillary column was used for separation of the test material from toluene. The gas chromatograph was calibrated with liquid standards of 3,6-Penta dissolved in toluene. Measured volumes of chamber air were drawn through an impinger containing toluene and the concentration interpolated from known standards. The analytical system was checked prior to each exposure with at least one standard of known concentration.

Prior to animal exposures the distribution of test material was determined from 4 sample points at the extremes of the animal breathing zone and the reference point within the chamber. The reference point was approximately 15 an from the breathing zone. The concentration of test material within the 4 sample locations for each chamber ranged from 77-139% from the mean reference mean value. Because of the relatively large range noted during the distribution check, each group of male and female mice was rotated daily within the chamber.

Chamber Concentration. Groups of 5 mice/sex were exposed to analytically measured concentrations of 0, 0.05, 0.32 and 1.35 ppm (0.0, 0.5, 3.5 and 14.6 micrograms/liter, respectively) 3,6-Penta for 6 hours/day, 5 days/week for 9 exposures (exposures occurred on test days 1-5 and 8-11). The highest concentration was the maximum practically attainable concentration. These exposure levels, 0.05, 0.32 and 1.35 ppm, corresponded to target concentrations of 0, 0.1, 0.5 and 1.5 ppm 3,6-

Penta. At the same time, these animals were also exposed to an impurity in the test material at concentrations as high as 0.01, 0.07 and 0.3 ppm 2,3-dichloro-6-trichloromethylpyridine.

Observations and Records. Each animal was examined ophthalmologically with a pen light prior to the initial exposure to 3,6-Penta; there were no significant ocular abnormalities noted. All animals were observed daily after exposure for overt signs of toxicity or changes in demeanor. These observations included an evaluation of the fur, eyes, mucous membranes and respiration. Behavior pattern and nervous system activity were assessed by specific observations for lethargy, tremors, convulsions, salivation, lacrimation, diarrhea and other signs of altered central nervous system function. An additional daily observation and routine monitoring on weekends were limited to animal husbandry procedures required to ensure the availability of food and water. All animals were weighed on test days 1, 3, 5,8, and 11.

Clinical Laboratory Determinations

Hematology. Blood samples were collected by orbital sinus puncture from mice anesthetized with methoxyflurane immediately prior to necropsy. The following hematologic parameters were evaluated for each animal with an Ortho ELT-8 (Ortho Instruments, Boston, MA): hematocrit (HCT), hemoglobin (HGB), erythrocyte count (RBC), total leukocyte (WBC) and platelet (PLAT) count. Slides for differential leukocyte counts were prepared for all animals. The differential count consisted of counting 100 leukocytes per animal on a Wright's stained blood smear. In addition, the morphology of the leukocytes, erythrocytes and platelets was assessed during the differential count.

Clinical Chemistry. Blood samples for serum analyses were collected at the terminal sacrifice from the orbital sinus of mice. Serum samples were chilled with crushed ice or refrigerated until analyzed. The following parameters were measured with a CentrifiChem automated chemistry analyzer (Baker Instruments Corp., Allentown, PA): urea nitrogen (UN), alanine aminotransferase activity (ALT), aspartate aminotransferase activity (AST), alkaline phosphatase activity (AP), glucose (GLUC), total protein (TP), albumin (ALE), globulin (GLOB), cholesterol (CHOL) and triglycerides (TRIG).

Pathology. All animals were necropsied the day following the last exposure to the test material. Mice were not fasted overnight prior to the scheduled necropsy. Each animal was weighed, anesthetized with methoxyflurane and humanely euthanized. Weights of the brain, heart, liver, kidneys and testes were recorded from all animals at the scheduled sacrifice. All animals were examined for gross pathological alterations by a veterinary pathologist. The necropsy included in situ examination of the eyes using a moistened glass-slide pressed against the corneal surface. A complete set of tissues was collected from each animal and preserved in neutral, phosphate-buffered 10% formalin. The lungs were infused with buffered formalin to their approximate normal inspiratory volume and the nasal cavities were flushed with formalin via the pharyngeal duct to insure rapid fixation.

A complete histopathologic examination of tissues listed was made from all animals in the control and highest exposure group. In addition, the livers from mice exposed to lower concentrations of test material were examined microscopically. Tissues were processed by conventional techniques, sectioned at approximately 6 microns, stained with hematoxylin and eosin and evaluated with light microscopy by a veterinary pathologist.

Statistical Evaluation. Descriptive statistics (mean and standard deviation) was used to report chamber concentrations, temperature and relative humidity and white blood cell differential counts.

All remaining parameters examined statistically were first tested for equality of variance using Bartlett's test. Since the equality of variance was not rejected in any parameter examined, each parameter was subjected to appropriate parametric analysis as described below. In-life body weight was evaluated using a three-way analysis of variance (ANOVA) with the factors of sex, dose and time interval (Winer, 1971). Hematology (excluding differential WBC) and clinical chemistry parameters, terminal body weight, organ weight (absolute and relative except testes) and urine specific gravity were evaluated using a two-way ANOVA with the factors of sex and dose (Winer, 1971). Results for absolute and relative testes weights were analyzed using a one way ANOVA. If significant dose effects were determined in the one-way ANOVA, then separate doses were compared to controls using Dunnett's test.

For those parameters examined by a two-way ANOVA, examination was made first for a significant sex-dose interaction, If this existed, a one-way ANOVA was done separately for each sex. If no sex-dose interaction was identified, and a dose effect was identified, or if in the subsequent ANOVA's separated by sex a dose effect was identified, then separate ANOVA's were used for each exposure group with control. To control for multiple comparisons with control, a Bonferroni correction was used.

The nominal alpha levels used and test references included:
One-Way ANOVA
Bartlett's test (Winer, 1971) a = 0.01
ANOVA (Steel and Torrie, 1960) a = 0.10
Dunnett's test (Winer, 1971) a = 0.05, two-sided

Two-Way ANOVA
Bartlett's test (Winer, 1971) a = 0.01
First ANOVA (Winer, 1971)
Sex-dose a = 0.05
Dose factor a=0.10
Second ANOVA (Winer, 1971)
Sex-dose a = 0.05
Dose factor a = 0.05

Three-Way ANOVA
Bartlett's test (Winer, 1971) a = 0.01
First ANOVA (Winer, 1971)
Time-sex-dose a = 0.01
Sex-dose a = 0.05
Sex-time a = 0.05
Time-dose a = 0.05
Dose a = 0.10

Second ANOVA (Winer, 1971)
Time-sex-dose a = 0.01
Sex-dose a = 0.05
Sex-time a = 0.05
Time-dose a = 0.05
Dose a = 0.05

Because numerous measurements are statistically compared in the same group of animals, the overall false positive rate (Type I errors) could be much greater than the above cited alpha levels might suggest. As a consequence, the final interpretation of numerical data considered statistical analyses along with other factors, such as dose-response relationships and whether the results were plausible in light of other biological and pathological findings.

1 Accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

Result : Animals were exposed to time-weighted average concentrations (TWA) of 0.05, 0.32 or 1.35 ppm of 3,6-Penta for 6 hours/day, 5 days/week for 9 exposures (Table 3). These concentrations corresponded to target concentrations of 0, 0.1, 0.5 and 1.5 ppm 3,6-Penta. The highest concentration, 1.35 ppm 3,6-Penta, was the maximum practically attainable concentration without aerosol formation in the chamber. The nominal concentration was approximately four times higher than the analytical concentration for each exposure level. As previously mentioned, the nominal concentration was calculated as accurately as possible. However, the lower calculation limit for nominal concentrations was 0.9 ppm due to the small amount of test material used each day and the heavy generation apparatus (4000 grams in weight) which required a balance with limited sensitivity (0.1 grams sensitivity). Temperature and relative humidity values for animals exposed to the various concentrations of 3,6-Penta were comparable to control values during the 2 week study.

MICE. All mice survived the 9 exposures to concentrations as high as 1.35 ppm 3,6-Penta with no overt signs of toxicity or changes in demeanor observed. The body weights of male and female mice exposed to 3,6-Penta were comparable to control values (Tables 21, 22 and 31).

Hematology and clinical chemistry values are presented in Tables 23-28 and
31. There were no exposure-related effects noted in any of these parameters in mice.

The terminal body weights and absolute and relative organ weights of male and female mice are presented in Tables 29-31, respectively. The absolute and relative liver weights of male and female mice exposed to 1.35 ppm 3,6-Penta were statistically significantly increased (absolute liver weights were increased 2.6 and 19.5%, respectively) from control values. AU other organ weight values were comparable to control values.

There were no exposure-related gross pathologic or histopathologic observations in mice (Tables 32 and 33). Although the absolute and relative liver weights of male and female mice exposed to 1.35 ppm 3,6-Penta were increased, this was not accompanied by any gross or microscopic changes indicative of an exposure-related effect. Several mice from the control and exposed groups had aspirated blood in their lungs secondary to the decapitation procedure. Microscopically, these mice had focal or multifocal areas of intraalveolar hemorrhage.

Source : The Dow Chemical Company, Midland, MI.
Conclusion : The No-Observed-Effect-Level (NOEL) in this study was considered to be 0.32 ppm 3,6-Penta.
Reliability : (1) valid without restriction
20.09.2004 (11)

5.5 GENETIC TOXICITY ‘IN VITRO‘

5.6 GENETIC TOXICITY ‘IN VIVO‘

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

Type : other: TOPKAT and DEREK QSAR Analysis

Attached document : 3 6-Dichlor-2-trichloromethylpyridine.doc
Chlorinated Pyridines.xls

08.12.2005

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

9. References

Id 1817-13-6
Date

(1) (Patent) Dow Chemical Co. BE 624800 1963 US, Chem. Abstr., 61(1841a)

(2) MPBPWIN v1.41, © 2000 U.S. EPA

(3) KOWWIN v1.67, © 2000 U.S. EPA

(4) WSKOWWIN v1.41, © 2000 U.S. EPA

(5) U.S. EPA, 2000. - AOPWin, v1.91, Atmospheric half-life estimating software & experimental value database.

(6) Mackay, D., 2001. Multimedia Environmental Models: The Fugacity Approach. Lewis Publishers, CRC Press, Boca Raton, FL. Models available at: http://www.trentu.ca/cemc/models.html

(7) U.S. EPA. (2004). EPI Suite software, version v3.12. United States Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D. C. Available at: http://www.epa.gov/oppt/exposure/docs/episuitedl.htm

(8) U.S. EPA, 2000. - BIOWin, v4.01, Biodegradation probability estimating software.

(9) U.S. EPA, 2000. - BCFWin, v2.15, Bioconcentration factor (BCF) estimating software.

(10) Unpublished data, The Dow Chemical Company, 1982.

(11) Unpublished data, The Dow Chemical Company.

10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

Chapter : Toxicity
Memo : Comparison of DEREK profiles for test material and Pentachloropyridine.

Remark : DEREK for Windows report

Date Created: Monday, December 08, 2003
Version: 7.0.0
Database: N:\Private\Lhasa Ltd\LPS 700\Dfw700.mdb
Database Version: DFW7.0.0_22_09_2003
Testing Against: All Alerts

Species: bacterium
mammal
Salmonella typhimurium
SuperEndpoints: Carcinogenicity
Genotoxicity
Irritation
Miscellaneous endpoints
Respiratory sensitisation
Skin sensitisation
Thyroid toxicity
Consider Tautomers: True
Hydrogen Options: Perceive implicit and explicit hydrogens
Override automatic Log P calculation: False
AutoSave: Off
AutoSave Directory: N:\Private\Lhasa Ltd\LPS 700\work
Name Field:

Compound Name: 2-Chloro-5-trichloromethylpyridine

Log Kp: -2.325 Calculated by the Potts & Guy equation
Log P: 2.54 Calculated by the Moriguchi estimation
Molecular Weight: 230.909 Calculated by LPS

Submitted Compound:

List of alerts found:

122 Di- to poly-halogenated alkane or cycloalkane. Carcinogenicity. Number of matches = 1
346 Trichloromethyl aromatic compound. Mutagenicity. Number of matches = 1

LHASA PREDICTIONS

Carcinogenicity

mammal - Reasoning

Carcinogenicity in mammal is PLAUSIBLE
[Carcinogenicity alert set 1] is [CERTAIN]
[Species dependent variable 22] is [PLAUSIBLE]
[alert 122] is [CERTAIN]
[species mammal] is [CERTAIN]

Alert overview: 122 Di- to poly-halogenated alkane or cycloalkane

Some halo-alkanes are alkylating agents, not needing metabolic activation. However, free-radical pathways have been postulated for 1,1,1-trihaloalkanes.

References:

Title: General principles for evaluating the safety of compounds used in food-producing animals.
Author: Food and Drug Administration (FDA).
Source: Food and Drug Administration Report, 1986, III-7-III-17, July 1994 revision available at "http://www.fda.gov/cvm/guidance/guideline3toc.html".

Locations:

Examples: (122 Di- to poly-halogenated alkane or cycloalkane)

(No examples)

Custom Examples: (122 Di- to poly-halogenated alkane or cycloalkane)

(No examples)

Mutagenicity

bacterium - Reasoning

Mutagenicity in vitro in bacterium is PLAUSIBLE
[alert 346] is [CERTAIN]
[species bacterium] is [CERTAIN]

Salmonella typhimurium - Reasoning

Mutagenicity in vitro in Salmonella typhimurium is PLAUSIBLE
[alert 346] is [CERTAIN]
[species bacterium] is [CERTAIN]

Alert overview: 346 Trichloromethyl aromatic compound

Mutagenicity: Ames test

This alert describes the mutagenicity of trichloromethyl aromatic compounds.

Compounds of this type generally exhibit mutagenicity in the Ames test, notably in Salmonella strains TA98 and TA100 in the presence, but not absence, of S9 [Zeiger et al 1988, 1992, Yasuo et al]. Trifluoromethyl aromatic compounds are not, however, mutagenic in the Ames test [Zeiger et al 1988, 1992, Haworth et al].

References:

Title: Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals.
Author: Zeiger E, Anderson B, Haworth S, Lawlor T and Mortelmans K.
Source: Environmental and Molecular Mutagenesis, 1992, 19 (supplement 21), 2-141.

Title: Salmonella mutagenicity test results for 250 chemicals.
Author: Haworth S, Lawlor T, Mortelmans K, Speck W and Zeiger E.
Source: Environmental Mutagenesis, 1983, 5 (supplement 1), 3-142.

Title: Salmonella mutagenicity tests: IV. Results from the testing of 300 chemicals.
Author: Zeiger E, Anderson B, Haworth S, Lawlor T and Mortelmans K.
Source: Environmental and Molecular Mutagenesis, 1988, 11 (supplement 12), 1-158.

Title: Mutagenicity of benzotrichloride and related compounds.
Author: Yasuo K, Fujimoto S, Katoh M, Kikuchi Y and Kada T.
Source: Mutation Research, 1978, 58, 143-150.

Locations:

Examples: (346 Trichloromethyl aromatic compound)

(No examples)

DEREK for Windows report

Date Created: Monday, December 08, 2003
Version: 7.0.0
Database: N:\Private\Lhasa Ltd\LPS 700\Dfw700.mdb
Database Version: DFW7.0.0_22_09_2003
Testing Against: All Alerts

Species: bacterium
mammal
Salmonella typhimurium
SuperEndpoints: Carcinogenicity
Genotoxicity
Irritation
Miscellaneous endpoints
Respiratory sensitisation
Skin sensitisation
Thyroid toxicity
Consider Tautomers: True
Hydrogen Options: Perceive implicit and explicit hydrogens

Override automatic Log P calculation: False
AutoSave: Off
AutoSave Directory: N:\Private\Lhasa Ltd\LPS 700\work
Name Field:

Compound Name: 2,3,4,5,6-pentachloropyridine

Log Kp: -2.45 Calculated by the Potts & Guy equation
Log P: 2.54 Calculated by the Moriguchi estimation
Molecular Weight: 251.327 Calculated by LPS

Submitted Compound:

List of alerts found:

438 Activated pyridine, quinoline or isoquinoline. Skin sensitisation.
Number of matches = 3

LHASA PREDICTIONS

Skin sensitisation

mammal - Reasoning

Skin sensitisation in mammal is PLAUSIBLE
[Skin sensitisation alert] is [CERTAIN]
[species mammal] is [CERTAIN]

Alert overview: 438 Activated pyridine, quinoline or isoquinoline

Electrophilic substituted pyridines, quinolines or isoquinolines may react with skin protein via a SnAr mechanism. Nucleophilic substitutions proceed slowly at aromatic carbons, but compounds of this type are susceptible to nucleophilic attack at the ring carbon attached to R1 in the presence of electron withdrawing groups in the ortho and para ring positions. The ring nitrogens can exert a strong activation, and may behave analogously to nitro groups on activated benzenes (alert 415). The activation is enhanced further if the ring nitrogen is positively charged as N-oxide or N-Me. The reactivity of these compounds is dependent on the combination of the strength of the leaving group R1, and the strength and number of the electron withdrawing groups R2 [Roberts, March, Landsteiner and Jacobs, De Boer and Dirkx].

The presence of a skin sensitisation structural alert within a molecule indicates the molecule has the potential to cause skin sensitisation. Whether or not the molecule will be a skin sensitiser will also depend upon its percutaneous absorption. Generally, small lipophilic molecules are more readily absorbed into the skin and are therefore more likely to cause sensitisation.

References:

Title: Studies on the sensitization of animals with simple chemical compounds. II.
Author: Landsteiner K and Jacobs J.
Source: Journal of Experimental Medicine, 1936, 64, 625-639.

Title: Annex to commission directive 93/72/EEC of 1 September 1993 adapting to technical progress for the nineteenth time council directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, ...
Author: Commission of the European Communities.
Source: Official Journal of the European Communities, 1993, 36 (L258A), 1-1409.

Title: Linear free energy relationships for reactions of electrophilic halo- and pseudohalobenzenes, and their application in prediction of skin sensitization potential for SnAr electrophiles.
Author: Roberts DW.
Source: Chemical Research in Toxicology, 1995, 8, 545-551.

Title: Aromatic nucleophilic substitution.
Author: March J.
Source: Advanced organic chemistry. Reactions, mechanisms, and structure, 3rd edition, March J, Wiley-Interscience, New York, 1985, 576-607.

Title: Activating effects of the nitro group in aromatic substitutions.
Author: De Boer TJ and Dirkx IP.
Source: The Chemistry of the nitro and nitroso groups. Part 1, Chapter 8, Feuer H (editor), Interscience Publishers, New York, 1969, 487-612.

Locations:

Examples: (438 Activated pyridine, quinoline or isoquinoline)

Example 1. 2-fluoro-5-trifluoromethylpyridine
CAS Number: 69045-82-5

Test Data: (2-fluoro-5-trifluoromethylpyridine)

1.
Species: unspecified
Assay: unspecified
Result: R43

References:

Title: Annex to commission directive 93/72/EEC of 1 September 1993 adapting to technical progress for the nineteenth time council directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, ...
Author: Commission of the European Communities.
Source: Official Journal of the European Communities, 1993, 36 (L258A), 1-1409.

Example 2. 2,3,5,6-tetrachloro-4-(methylsulphonyl)pyridine
CAS Number: 13108-52-6

Test Data: (2,3,5,6-tetrachloro-4-(methylsulphonyl)pyridine)

1.
Species: unspecified
Assay: unspecified
Result: R43

References:

Title: Commission directive 94/69/EC of 19 December 1994 adapting to technical progress for the twenty-first time council directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging ...
Author: Commission of the European Communities.
Source: Official Journal of the European Communities, 1994, 37 (L381), 1-1485.

Source : The Dow Chemical Company, Midland, MI.
Reliability : (2) valid with restrictions
20.09.2004

10.3 RISK ASSESSMENT

201-16113

RECEIVED
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05 DEC 27 AM 9:48

I U C L I D

Data Set

Existing Chemical	: ID: 68412-40-8
CAS No.	: 68412-40-8
Generic name	: Chloropyridine Derivatives

Producer related part

Company	: The Dow Chemical Company
Creation date	: 27.09.2004

Substance related part

Company	: The Dow Chemical Company
Creation date	: 27.09.2004
Status	:
Memo	:
Printing date	: 27.09.2004
Revision date	:
Date of last update	: 27.09.2004
Number of pages	: 16
Chapter (profile)	: Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	: Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	: Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	manufacturer
Name	:	Dow Agrosciences PLC
Contact person	:	
Date	:	
Street	:	9330 Zionsville Road
Town	:	46268 Indianapolis, IN
Country	:	United States
Phone	:	(+1) 317-337-3890
Telefax	:	(+1) 317-337-4444
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
27.09.2004

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

Remark : Chloropyridine derivatives (CAS No. 68412-40-8) is a stream containing members of a group of chemicals known as chloropyridines, used in the production of chlorinated pesticides. The composition of the stream varies in relative proportion, but not identity of components. A major component of this stream is pentachloropyridine (CAS No. 2176-62-7).
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
27.09.2004

1.1.1 GENERAL SUBSTANCE INFORMATION

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

2.2 BOILING POINT

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

2.5 PARTITION COEFFICIENT

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Chloropyridine derivatives is a stream containing chloropyridines. This stream varies by proportion of, but not nature of, component. Thus, determination of consistent physical properties is not possible for this stream.

Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
27.09.2004

3.1.1 PHOTODEGRADATION

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

5.5 GENETIC TOXICITY ‘IN VITRO‘

5.6 GENETIC TOXICITY ‘IN VIVO‘

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

9. References

10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

Chapter : Toxicity

Remark : In an effort to reduce animal testing and to leverage existing data, published and unpublished data for 2,3,4,5,6-pentachloropyridine (CAS No. 2176-62-7), as detailed in the Robust Summaries, will be used as a surrogate to satisfy the requirements of all required mammalian testing. This material is component of the chloropyridine derivatives stream, and the safe handling procedures detailed for pentachloropyridine are conservatively estimated to provide adequate protection from the derivatives stream. Additional testing would be unlikely to change safe handling recommendations for the derivatives stream. Thus, the Robust Summaries provide adequate data to characterize the human health effects endpoints under the Program.

Source : The Dow Chemical Company, Midland, MI.

Reliability : (2) valid with restrictions

The comparison of this stream with pentachloropyridine and the use of pentachloropyridine data as surrogate data for this stream is in keeping with current hazard assessment methods and practices.

27.09.2004

Chapter : Environmental Fate and Pathways

Remark : In an effort to reduce testing and to leverage existing data, published and unpublished data for 2,3,4,5,6-pentachloropyridine (CAS No. 2176-62-7), as detailed in the Robust Summaries, will be used as a surrogate to satisfy the requirements of all required environmental fate testing. This material is component of the chloropyridine derivatives stream, and the safe handling procedures detailed for pentachloropyridine are conservatively estimated to provide adequate protection from the derivatives stream. Additional testing would be unlikely to change safe handling recommendations for the derivatives stream. In addition, current practice in environmental fate assessment recognizes that components of a mixture characteristically behave as individual components in the environment. Thus, the Robust Summaries provide adequate data to characterize environmental fate endpoints under the Program.

Source : The Dow Chemical Company, Midland, MI.

Reliability : (2) valid with restrictions

The comparison of this stream with pentachloropyridine and the use of pentachloropyridine data as surrogate data for this stream is in keeping with current hazard assessment methods and practices.

27.09.2004

Chapter : Ecotoxicity

Remark : In an effort to reduce testing and to leverage existing data, published and unpublished data for 2,3,4,5,6-pentachloropyridine (CAS No. 2176-62-7), as detailed in the attached Robust Summaries, will be used as a surrogate to satisfy the requirements of all required ecotoxicity testing. This material is component of the chloropyridine derivatives stream, and the safe handling procedures detailed for pentachloropyridine are conservatively estimated to provide adequate protection from the derivatives stream. Additional testing would be unlikely to change safe handling recommendations for the derivatives stream. Thus, the Robust Summaries provide adequate data to characterize the ecotoxicity endpoints under the Program.

Source : The Dow Chemical Company, Midland, MI.

Reliability : (2) valid with restrictions

The comparison of this stream with pentachloropyridine and the use of pentachloropyridine data as surrogate data for this stream is in keeping with current hazard assessment methods and practices.

27.09.2004

10.3 RISK ASSESSMENT

201-16113

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05 DEC 27 AM 9:48

I U C L I D

Data Set

Existing Chemical	:	ID: 70024-85-0
CAS No.	:	70024-85-0
Generic name	:	Methyl chloropyridine derivatives

Producer related part

Company	:	The Dow Chemical Company
Creation date	:	27.09.2004

Substance related part

Company	:	The Dow Chemical Company
Creation date	:	27.09.2004
Status	:	
Memo	:	
Printing date	:	27.09.2004
Revision date	:	
Date of last update	:	27.09.2004
Number of pages	:	16
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	manufacturer
Name	:	Dow Agrosciences PLC
Contact person	:	
Date	:	
Street	:	9330 Zionsville Road
Town	:	46268 Indianapolis, IN
Country	:	United States
Phone	:	(+1) 317-337-3890
Telefax	:	(+1) 317-337-4444
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

27.09.2004

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

Remark	:	Methyl chloropyridine derivatives (CAS No. 70024-85-0) is a stream containing members of a group of chemicals known as chloropyridines, used in the production of chlorinated pesticides. The composition of the stream varies in relative proportion, but not identity of components. A major component of this stream is pentachloropyridine (CAS No. 2176-62-7).
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

27.09.2004

1.1.1 GENERAL SUBSTANCE INFORMATION

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

2.2 BOILING POINT

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

2.5 PARTITION COEFFICIENT

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Methyl chloropyridine derivatives is a stream containing chloropyridines. This stream varies by proportion of, but not nature of, component. Thus, determination of consistent physical properties is not possible for this stream.

Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
27.09.2004

3.1.1 PHOTODEGRADATION

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

5.5 GENETIC TOXICITY ‘IN VITRO‘

5.6 GENETIC TOXICITY ‘IN VIVO‘

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

9. References

Id 70024-85-0
Date 27.09.2004

10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

Chapter : Toxicity

Remark : In an effort to reduce animal testing and to leverage existing data, published and unpublished data for 2,3,4,5,6-pentachloropyridine (CAS No. 2176-62-7), as detailed in the Robust Summaries, will be used as a surrogate to satisfy the requirements of all required mammalian testing. This material is component of the methyl chloropyridine derivatives stream, and the safe handling procedures detailed for pentachloropyridine are conservatively estimated to provide adequate protection from the derivatives stream. Additional testing would be unlikely to change safe handling recommendations for the derivatives stream. Thus, the Robust Summaries provide adequate data to characterize the human health effects endpoints under the Program.

Source : The Dow Chemical Company, Midland, MI.

Reliability : (2) valid with restrictions
The comparison of this stream with pentachloropyridine and the use of pentachloropyridine data as surrogate data for this stream is in keeping with current hazard assessment methods and practices.

27.09.2004

Chapter : Environmental Fate and Pathways

Remark : In an effort to reduce testing and to leverage existing data, published and unpublished data for 2,3,4,5,6-pentachloropyridine (CAS No. 2176-62-7), as detailed in the Robust Summaries, will be used as a surrogate to satisfy the requirements of all required environmental fate testing. This material is component of the methyl chloropyridine derivatives stream, and the safe handling procedures detailed for pentachloropyridine are conservatively estimated to provide adequate protection from the derivatives stream. Additional testing would be unlikely to change safe handling recommendations for the derivatives stream. In addition, current practice in environmental fate assessment recognizes that components of a mixture characteristically behave as individual components in the environment. Thus, the Robust Summaries provide adequate data to characterize environmental fate endpoints under the Program.

Source : The Dow Chemical Company, Midland, MI.

Reliability : (2) valid with restrictions
The comparison of this stream with pentachloropyridine and the use of pentachloropyridine data as surrogate data for this stream is in keeping with current hazard assessment methods and practices.

27.09.2004

Chapter : Ecotoxicity

Remark : In an effort to reduce testing and to leverage existing data, published and unpublished data for 2,3,4,5,6-pentachloropyridine (CAS No. 2176-62-7), as detailed in the attached Robust Summaries, will be used as a surrogate to satisfy the requirements of all required ecotoxicity testing. This material is component of the methyl chloropyridine derivatives stream, and the safe handling procedures detailed for pentachloropyridine are conservatively estimated to provide adequate protection from the derivatives stream. Additional testing would be unlikely to change safe handling recommendations for the derivatives stream. Thus, the Robust Summaries provide adequate data to characterize the ecotoxicity endpoints under the Program.

Source : The Dow Chemical Company, Midland, MI.

Reliability : (2) valid with restrictions
The comparison of this stream with pentachloropyridine and the use of pentachloropyridine data as surrogate data for this stream is in keeping with current hazard assessment methods and practices.

27.09.2004

10.3 RISK ASSESSMENT

201-16113

RECEIVED
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IUCLID

Data Set

Existing Chemical	:	ID: 2176-62-7
CAS No.	:	2176-62-7
Common name	:	2,3,4,5,6-Pentachloropyridine

Producer related part

Company	:	The Dow Chemical Company
Creation date	:	20.05.2002

Substance related part

Company	:	The Dow Chemical Company
Creation date	:	20.05.2002
Status	:	
Memo	:	
Printing date	:	08.12.2005
Revision date	:	
Date of last update	:	08.12.2005
Number of pages	:	37
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1. General Information

Id 2176-62-7
Date

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	
Name	:	Dow AgroSciences
Contact person	:	
Date	:	
Street	:	9330 Zionsville Road
Town	:	Indianapolis, IN 46268-1189
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

04.06.2002

Type	:	
Name	:	The Dow Chemical Company
Contact person	:	
Date	:	
Street	:	2020 Dow Center
Town	:	48674 Midland, Michigan
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

20.05.2002

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

Type	:	
Name of plant	:	
Street	:	
Town	:	Freeport, TX
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

04.06.2002

Type	:	
Name of plant	:	
Street	:	
Town	:	Pittsburg, CA
Country	:	United States
Phone	:	
Telefax	:	

Telex :
Cedex :
Email :
Homepage :

04.06.2002

1.0.3 IDENTITY OF RECIPIENTS

Name of recipient : The Dow Chemical Company
Street :
Town : Freeport, TX
Country : United States
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

04.06.2002

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type :
Substance type : inorganic
Physical status : solid
Purity : > 99 % w/w
Colour :
Odour :

Test substance : Molecular formula = C5Cl5N
Molecular weight = 251.3
Substance Type = organic
Physical status = white solid
Odor = sharp pyridine-like

04.06.2002

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

:Pentachloropyridine

20.05.2002

PCP

04.06.2002

1.3 IMPURITIES

Purity :
CAS-No :
EC-No :
EINECS-Name : 2,5,6-trichloro-3-pyridinecarboxylic acid
Molecular formula :
Value :

04.06.2002

Purity :
CAS-No : 2808-86-8
EC-No :
EINECS-Name : Tetrachloropyridine
Molecular formula :
Value : = .4 % w/w

04.06.2002

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : 10 - 50 tonnes produced in

04.06.2002

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : type
Category : Non dispersive use

Remark : 1) 75 % used in the manufacturing of Symtet
2) 24.9 % sent to Freeport, Texas
3) 0.1% sent to external customers

04.06.2002

Type of use : type
Category : Use in closed system

04.06.2002

Type of use : industrial
Category : Agricultural industry

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Type of use : industrial
Category : other: pharmaceutical industry

04.06.2002

Type of use : use
Category : Intermediates

04.06.2002

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : other: Dow AgroSciences Industrial Hygiene Guide
Limit value : 7 mg/m3

04.06.2002

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Remark : Sampling conducted using Proper Protective Equipment per the MSDS recommendation.
Sources of Exposure
This chemical is produced in Pittsburg, California and is shipped to Freeport, Texas. Therefore, chemical is present at two sites. The chemical known as PCP is an intermediate in the production of Symtet and Starane Herbicide. Chlorine and Picolines are reacted in a vapor phase reactor followed by a series of liquid phase reactors. This material is then distilled with the PCP product stored in a tank prior to loading into a rail car. The unreacted material is recycled back to the reactors and reprocessed. The system is fully contained with no atmospheric vents. Vents are collected and sent to a vent condenser followed by thermal incineration or caustic scrubber. The scrubber effluent is sent to a Chlorinolysis facility for treatment and disposal. We have in process flow meters that perform material balances to ensure and track that PCP volumes do not escape into the environment. PCP is present in the Symtet intermediate at the 0.1 - 0.6 wt% level. PCP is not present in the end-use products of Garlon (Triclopyr) or Chlorpyrifos. PCP is also present in N-Serve 24 at the 0.2 - 0.44 wt% levels. This is an end use product.

04.06.2002

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= 125 - 126 °C
Sublimation	:	
Method	:	
Year	:	1982
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Measured value

04.06.2002 (1)

2.2 BOILING POINT

Value	:	= 273 °C at
Decomposition	:	
Method	:	other: calculated
Year	:	2002
GLP	:	
Test substance	:	

04.06.2002 (2)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Decomposition	:	
Method	:	other (measured)
Year	:	1967
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	0.014 mm Hg at 25 0C

04.06.2002 (3)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	
Log pow	:	= 3.53 at °C
pH value	:	
Method	:	other (measured)
Year	:	1967
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

04.06.2002 (3)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in :
Value : = 8.5 mg/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : slightly soluble (0.1-100 mg/L)
Stable :
Deg. product :
Method : other: measured
Year : 1982
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : Dissociation Constant: Not applicable. Does not ionize within environmentally relevant pH ranges.

04.06.2002 (4)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

INDIRECT PHOTOLYSIS

Sensitizer : OH
Conc. of sensitizer : 1500000 molecule/cm³
Rate constant : = .000000000000011 cm³/(molecule*sec)
Degradation : ca. 50 % after 974 day(s)

Source : The Dow Chemical Company, Midland, MI.
05.06.2002 (5)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product :
Method : other (calculated)
Year : 2002
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Because the test material does not ionize at environmentally relevant pH ranges, no rate constants could be calculated for stability in water.
Reliability : (1) valid without restriction
12.09.2003 (6)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level III
Media : other
Air : 73.55 % (Fugacity Model Level I)
Water : 6.5 % (Fugacity Model Level I)
Soil : 19.5 % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other
Year : 2003

Method : Test: Environmental Distribution and Transport between Environmental Compartments
Method: Level I and Level III Fugacity Models.
Year: 2003
Remarks: Level I model version 2.11, Level III model version 2.70.

Obtained from the Canadian Environmental Modeling Centre, Trent University, Peterborough, Ontario, Canada

Input Parameters for Level I Model:
Property Value Source
Data Temperature (°C) 25
Chemical Type 1 Type 1 indicates
chemical can partition into all environmental
compartments
Molecular Mass (g/mol) 251.33 Calculated from
molecular structure
Water Solubility (g/m3) 8.5 Measured value
Vapor Pressure @ 25°C
(Pa) 1.9 Measured value
Melting Point (°C) 125 Measured value
Log Kow
Octanol-Water
Partition Coefficient 3.53 Measured value
Amount of Chemical
input (kg) 100,000 Level I Default Value

Input Parameters for Level III Model:
Property Value Source
Data Temperature (°C) 25
Chemical Type 1 Type 1 indicates
chemical can partition into all environmental
compartments
Molecular Mass (g/mol) 251.33 Calculated from molecular
structure
Water Solubility (g/m3) 8.5 Measured value
Vapor Pressure @ 25°C
(Pa) 1.9 Measured value
Melting Point (°C) 125 Measured value
Estimated Henry's
Law Constant (H)
(Pa m3/mol) 56.1 Calculated by Level I
Fugacity Model
Log Kow
Octanol-Water
Partition Coefficient 3.53 Measured value
Amount of Chemical
input (kg/hr) 1,000 per Level III Default Values
compartment
Reaction Half-lives
(hr.) Input to Level
III Model
Air (vapor phase) 11700 Estimated value
Water(no susp. solids) *1.0 x 1011
Soil *1.0 x 1011
Sediment *1.0 x 1011
Suspended Sediment *1.0 x 1011
Fish *1.0 x 1011
Aerosol *1.0 x 1011

*Default value used in Level III model when reaction is expected to be negligible in this compartment

Result : Fugacity Level I: Distribution among air, water, soil, and sediments
Percentage and amount distributed to
Emission Scenario Air Water Soil Sediment
100,000 kg
total emissions 73.55 % 6.50% 19.50 % 0.43 %
73550 kg 6499 kg 19502 kg 433 kg

Fugacity Level III: Distribution among air, water, soil, and sediments
Percentage and amount distributed to
Emission Scenario Air Water Soil Sediment

1,000 kg/hr to Air 81.90 % 1.10 % 17.0 % 0.05 %
2000 kg 26.9 kg 415 kg 1.21 kg

1,000 kg/hr to Water 0.33 % 95.3 % 0.07 % 4.28 %
1266 kg 3.66 E+5 kg 262 kg 16452 kg

1,000 kg/hr to Soil 0.03 % 0.55 % 99.4 % 0.02 %
1927 kg 36328 kg 6.58 E+6 kg 1631 kg

1,000 kg/hr simultaneously to Air, Water, and Soil 0.07 % 5.75 % 93.9 % 0.26 %
5193 kg 4.03 E+5 kg 6.58 E+6 kg 18084 kg

Residence Time (days) [without advection in brackets]

0.10
[859]
16
[2.14E+5]
276
[2.42E+6]
97.3
[9.49 x 105]

Source : The Dow Chemical Company, Midland, MI.

Conclusion : Pentachloropyridine has a moderate potential to volatilize from aqueous solution, based on the estimated Henry's Law constant (56.1 Pa m3/mol). The compound has a moderate
potential to bioaccumulate in aquatic organisms based on the log Kow value (3.53).
Assuming an equal input of pentachloropyridine into air, water and soil, the Level III fugacity model predicts that most of the compound (94%) will move to the soil
compartment.

Reliability : (1) valid without restriction

21.09.2004 (7)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

3.6 BOD5, COD OR BOD5/COD RATIO

COD

Method	:	other: ThOD
Year	:	1975
COD	:	= .64 mg/g substance
GLP	:	no

Method : The theoretical oxygen demand is computed by assuming all carbon is oxidized to CO_2 and the hydrogen to H_2O. TODs are values obtained using the Dow Total Oxygen Demand Analyzer (Clifford, 1968). The oxygen demand is obtained by comparing peak heights of the sample to those of a known standard solution (standard potassium acid phthalate). TOD values are usually very close to the theoretical oxygen demand of the material.

12.09.2003 (8) (7)

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	= .28 measured/nominal
LC50	:	= .47 calculated
LC100	:	= .66 measured/nominal
Limit test	:	
Analytical monitoring	:	yes
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : Test Chemical

Test chemical was supplied by Aldrich Chemical Co., with a purity of 98% as determined by gas-liquid chromatography/mass spectrometry (GC/MS).

Analytical Technique

Gas-liquid chromatography was used to analyze toxicants in water samples from the fish exposure tanks. All compound analyses included one spike and one duplicate sample for every 6-12 water samples. Calibration curves were established by linear regression analysis of from 3-5 standards. Peak areas were used.

All test chambers were sampled at approximately mid-depth at 0, 24, 48, 72, and 96 hours in all exposure chambers. All samples were analyzed immediately or adequately preserved for later analysis.

Water Quality

Five water quality parameters were routinely measured. They were: water temperature, dissolved oxygen, total hardness, total alkalinity, and pH.

Water temperature was determined using a partial immersion thermometer. Measurements were made in each exposure chamber daily. The desired test temperature was 25 +/- 1 degree C.

Dissolved oxygen was determined in high, medium, low, and control exposure chambers at least once during the test. Daily measurements were taken in five treatments and the control exposure chambers during a 96-hour test if surviving fish existed in those chambers. Determinations were made with an oxygen-sensitive electrode (Yellow Springs Instrument, Yellow Springs, OH, Model 54 polarograph) which was calibrated weekly using the azide modification of the Winkler method.

Total hardness and total alkalinity measurements were made on the control (~45 mg/L as $CaCO_3$) and low, medium and high chambers were sampled once during the exposure duration.

pH was measured daily in the control and five treatment chambers. Measurements were made with a meter, calibrated prior to each test.

The test was conducted at the USEPA Environmental Research Laboratory-Duluth, using Lake Superior water which was filtered through sand and a cotton fiber filter.

Test Fish

Fathead minnows used in the test were cultured at the USEPA Environmental Research Laboratory-Duluth. Adults were held at 25 degrees C. in flowing water with a 16-hour light-controlled photoperiod and fed frozen adult brine shrimp (Artemia sp.) They were provided with asbestos pipes (cut in half longitudinally) as spawning substrates. The naturally spawned and fertilized embryos became attached to the underside of the spawning substrates. The substrates, with intact embryos, were removed daily and placed in another 25 degree C. bath where hatching occurred.

Fish were reared in flow-through tanks in the lab's culture units using water from the same source as that used in the test. Larvae were fed 40-48 hour old brine shrimp nauplii in excess two times daily (once on weekend days).

Fish approximately 26 to 37 days old were used in the toxicity test. Only groups of fish having a healthy appearance and no history of unusual thermal exposure or abnormally high mortality rate were used for toxicant exposure. Test fish were not fed 24 hours before or during a test.

Fish were randomly assorted to treatment chambers from a pooled group. Dose levels tested were 0, 0.28, 0.43, 0.66, 1.02, and 1.57 mg/L.

Death was the major test endpoint. The number of dead fish were noted every 24 hours after the beginning of a test, at which time they were also removed. Observations of fish behavior and toxic signs were made at 2-8, 24, 48, 72, and 96 hours. Unique behavior was also recorded using a color video camera and 0.5" tape recorder.

Individual control fish were weighed (wet weight) and measured (standard length). Four surviving fish each from the control, the lowest concentration and the concentration nearest the LC50 were preserved in 10% buffered formalin for histological examination.

Result : The 96 hour LC50 was approximately 0.47 mg/L, with confidence limits of 0.44-0.50. Affected fish lost schooling behavior and swam near the tank surface. They were hypoactive and underreactive to external stimuli, had increased respiration, were hemmorhagic and deformed, had rigid musculature, and lost equilibrium prior to death.

Source : The Dow Chemical Company, Midland, MI.

Reliability : (1) valid without restriction

19.09.2003 (9)

Type : static
Species : Notropis atherinoides
Exposure period : 72 hour(s)
Unit : mg/l
LC0 : = 1 measured/nominal
LC50 : = 1.23 calculated
LC100 : = 2 measured/nominal
Limit test :
Analytical monitoring : no
Method : other
Year : 1972
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Lake Emerald shiners were exposed to 1.0, 1.5, or 2.0 mg/L PCP for 72 hours in dechlorinated Lake Huron water at 50 deg. F. under static conditions.

04.06.2002 (10)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Crangon septemspinosa (Crustacea)
Exposure period : 43 hour(s)
Unit : mg/l
EC50 : = 1.8
Analytical monitoring : yes
Method : other
Year : 1979
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Shrimp, collected locally in St. Andrews, New Brunswick, Canada, were held in running sea water at 10 degrees C and 30 ppt salinity for at least a week before tests. They were fed brine shrimp and clams at 2-day intervals. They ranged in length from 6.4 to 8.3 cm (2.4 to 4.5 g).

A lethality test of 96 hours duration was carried out on three shrimp in 4 liters of aerated sea water at 10 degrees C, with the solution changed at 48 hours. A stock solution was prepared in either ethanol or dimethyl sulfoxide. From the stock solution, 5 dilutions were prepared such that 1 ml added to 4 L sea water produced the required test concentration. The control test contained 1 ml of ethanol or dimethyl sulfoxide in 4 liters of sea water, as appropriate.

Concentration of the test material was measured by UV spectrophotometry at the beginning and immediately after the solution change at 48 hours. In addition, the concentration of one solution of intermediate nominal concentration was measured at 2, 4, 6, 12, 24, and 48 hours.

The time to 50% mortality (LT50) at a particular concentration of a chemical was read from a plot of percentage mortality against time to death (logarithmic scales). Lethality lines were drawn from plots of LT50 against test concentration (logarithmic scales). The 96 hour threshold was taken as the geometric mean of the highest concentration with no deaths and the next higher concentration (step by a factor of 2) at which all three shrimp died.
Result : The measured concentration of the test material remained practically constant throughout the 48 hours. The highest dose level tested was 6 mg/l. The LC50 was calculated as 1.8 mg/l at 43 hours.
Source : The Dow Chemical Company, Midland, MI
Reliability : (1) valid without restriction
26.09.2003 (11)

Type : static
Species : other aquatic mollusc: soft-shelled clam (Mya arenaria)
Exposure period : 96 hour(s)
Unit : mg/l
NOEC : = 6 measured/nominal
EC50 : > 6 measured/nominal
Analytical monitoring : yes
Method : other
Year : 1979
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Clams, collected locally in St. Andrews, New Brunswick, Canada, were held in running sea water at 4 degrees C and 30 ppt salinity for at least a week before tests. They were uniform in size, measuring about 5 cm in length (20 g).

A lethality test of 96 hours duration was carried out on three clams in 4 liters of aerated sea water at 10 degrees C, with the solution changed at 48 hours. A stock solution was prepared in either ethanol or dimethyl sulfoxide. From the stock solution, 5 dilutions were prepared such that 1 ml added to 4 L sea water produced the required test concentration. The control test contained 1 ml of ethanol or dimethyl sulfoxide in 4 liters of sea water, as appropriate.

Concentration of the test material was measured by UV spectrophotometry at the beginning and immediately after the solution change at 48 hours. In addition, the concentration of one solution of intermediate nominal concentration was measured at 2, 4, 6, 12, 24, and 48 hours.

The time to 50% mortality (LT50) at a particular concentration of a chemical was read from a plot of percentage mortality against time to death (logarithmic scales). Lethality lines were drawn from plots of LT50 against test concentration (logarithmic scales). The 96 hour threshold was taken as the geometric mean of the highest concentration with no deaths and the next higher concentration (step by a factor of 2) at which all three clams died.

Result : The measured concentration of the test material remained practically constant throughout the 48 hours. The highest dose level tested was 6 mg/l. No mortality was observed throughout the 96 hour test period, so the LC50 was greater than 6 mg/l.
Source : The Dow Chemical Company, Midland, MI
Reliability : (1) valid without restriction
26.09.2003 (11)

Type : static
Species : other: ciliate protozoan, Tetrahymena pyriformis
Exposure period :
Unit :
Method :
Year : 1989
GLP :
Test substance :

04.06.2002 (12)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Selenastrum capricornutum (Algae)
Endpoint : biomass
Exposure period : 96 hour(s)
Unit : mg/l
NOEC : = 1 measured/nominal
EC50 : = 2.03 measured/nominal
Limit test :
Analytical monitoring : yes
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 2004
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Testing Facility
The testing was conducted by the Toxicology & Environmental Research

and Consulting Laboratory, The Dow Chemical Company, Midland, Michigan.

Test Substance
The sample of pentachloropyridine was supplied by Dow AgroSciences LLC, Indianapolis, Indiana. Information on the test material is summarized below [7,8].

Test Substance Number: TSN103958 [7]
Chemical Name: 2,3,4,5,6-Pentachloropyridine [7]
Common Name: Pentachloropyridine, K-039636, LSN061122 [7]
Synonyms: Pentachloropyridine
Lot Number: T-171C [7]
Physical State: Solid [7]
Purity: > 99% [8]
Reference Substance - Analytical Standard
Same as test material listed above

Culture and Test Medium
The culture conditions are listed in Table 1. The growth and test medium used was that designed for the EPA Algal Assay Bottle Test [9]. A complete description of the algal
assay medium (AAM) is provided in Appendix B.

Test Organism
Axenic samples of Pseudokirchneriella subcapitata (formerly known as Selenastrum capricornutum) were received on 13 February 2003 from the University of Toronto Culture Collection at the University of Toronto, Toronto, Ontario, Canada. Stock cultures of this organism were maintained aseptically by weekly transfer into sterile AAM.

Test Vessels
Test vessels were sterilized 250-mL borosilicate Erlenmeyer flasks with Shimadzu closures, each containing 100 mL test medium. Each flask was labeled with a unique number for identification purposes.

Algal Inoculum
The algal inoculum was prepared from a 3-day old stock culture of Pseudokirchneriella subcapitata. A Coulter Multisizer 3 was used to determine the algal density of the stock culture. This evaluation determined the aliquot of the culture required so that each test vessel would contain approximately 10,000 cells/mL (0.790 mL).

Dose Level Selection
The dose levels selected for evaluating the effects of pentachloropyridine on the growth of Pseudokirchneriella subcapitata were based on the results of a probe test and the preliminary solubility work of the compound in AAM. The solubility of pentachloropyridine in AAM with an acetone carrier (using = 0.1 mL acetone carrier/L media) was evaluated and determined to be approximately 1.0 to 5.0 mg
pentachloropyridine/L AAM. The probe test was conducted between 16 October and 20 October 2003 using four nominal pentachloropyridine concentrations of 0.008, 0.04, 0.2,
and 1.0 mg/L, plus a medium and solvent control. Percent inhibition compared to controls was -7, -3, -2, and 27% for the 0.008, 0.04, 0.2, and 1.0 mg/L test levels, respectively (negative percent inhibition values indicate stimulation of growth).

The definitive test levels were set at target concentrations of 0 (control), 0 (solvent control), 0.125, 0.250, 0.500, 1.00, 2.00, and 4.00 mg pentachloropyridine/L AAM. The 2.00 and 4.00 test concentrations were within the approximate range of solubility of pentachloropyridine in AAM.

The probe determined a response of 27% inhibition at the target concentration of 1.00 mg/L. Based on this, the addition of the 2.00 and 4.00 mg/L dose concentrations would possibly allow the determination of an EC50 value.

Test Solutions
Since the test material had low inherent solubility, an organic solvent (acetone) was used to aid in dissolution of the test material in AAM. Stock solutions were prepared at the following concentrations in acetone: 40, 20, 10, 5.0, 2.5, and 1.25 mg/mL. Pentachloropyridine was weighed out directly for the three highest concentration stock solutions. To prepare the 40, 20, and 10 mg/mL stock solutions, 80.15, 40.87, and 20.58 mg of pentachloropyridine, respectively, were dissolved into 2 mL of acetone. To prepare the 5.0, 2.5, and 1.25 mg/mL stock solutions, 1.0 mL of the next highest stock solution was diluted with 1.0 mL of acetone, respectively. The 4.00, 2.00, 1.00, 0.500, 0.250, and 0.125 mg pentachloropyridine/L test solutions were prepared by addition of 50 µL of the 40, 20, 10, 5.0, 2.5, and 1.25 mg/mL stock solutions, respectively, into approximately 400 mL of AAM in a 500-mL volumetric flask. The flasks were stoppered, mixed thoroughly, unstoppered, filled to the mark (500 mL) with AAM, restoppered, and mixed again. Following addition of the stock solution to the AAM during preparation of the 4.00 mg/L test solution, a powdery film was observed on the surface of the water. This solution was sonicated for approximately three minutes, which appeared to dissolve the precipitate into the media. Test solutions
were then dispensed to the appropriate test vessels.

Sample Collection and Analysis
The bulk dose solutions were sampled for analytical confirmation on day 0 of the study immediately following preparation. On day 4, the three test solutions containing algae at each dose level were pooled to provide one composite algae-containing sample per dose level for analytical confirmation. The test solutions at each dose level containing no algae were sampled separately. A 4-mL aliquot was collected from each test solution and
centrifuged for 10 minutes at 2000 rpm. The day 0 samples were centrifuged in order to maintain consistency with the day 4 sample preparation, although there was no algae in
the day 0 bulk dose solutions. A 1-mL aliquot of the supernatant was transferred to 4-dram vials and extracted with 10-mL iso-octane by shaking on a flat-bed shaker (low
speed) for 30 minutes followed by 10 minutes of centrifuging at 2000 rpm. For the control, solvent (acetone) control, 0.125, 0.250, and 0.500 mg/L solutions, a 100-µL aliquot of the extract was transferred to autosampler vials containing 0.9-mL iso-octane. For the 1.00, 2.00, and 4.00 mg/L solutions, a 10- µL aliquot of the extract was transferred to autosampler vials containing 1 mL of iso-octane. The samples were mixed with vortexing and analyzed using gas chromatography with an electron capture detector (GC/ECD).

Method Precision and Homogeneity
To assess analytical method precision and solution homogeneity, three additional samples were taken on day 0 from bulk dose solutions at nominal concentrations of 0.125 and 4.00 mg/L. These additional samples were prepared for analysis as described above and analyzed along with the other day 0 samples.

Extraction Efficiency of Pentachloropyridine from Algal Assay Media
The recovery (extraction efficiency) of pentachloropyridine from AAM by solventpartitioning with iso-octane was determined by fortifying AAM with pentachloropyridine
at concentrations representative of the expected range of dose solutions

and then conducting the extraction as described in Sample Collection/Extraction. Triplicate
spikes at of pentachloropyridine in AAM were prepared at target concentrations of ~ 0.1, 0.5, and 4 mg/L AAM. This assessment of extraction efficiency yielded average
recovery values of 95.4% for day 0 and 103% for day 4, which were used to adjust the analyzed concentrations of the test solutions for method recovery on each analysis day as needed.

Standard Preparation/Detector Calibration
Primary stock solutions of pentachloropyridine were prepared in acetone at nominal concentrations of ~ 200 mg pentachloropyridine/L for each analysis. The stock solutions were further diluted and used to prepare analytical standards in iso-octane over concentration ranges extending from ~ 0.1 to 6 µg pentachloropyridine/L, which encompassed the expected sample concentration range (after accounting for dilution during the sample preparation). Standards were analyzed with each set of samples to define the detector response.

Response factors calculated for each of the individual analytical standards were averaged to yield an overall mean response factor and standard deviation for each daily set of analyses. The measured concentrations (mg pentachloropyridine/L AAM) of the test solutions were then calculated as follows:
Response Factor (RF) = Standard Pentachloropyridine Concentration/Peak Area
Sample Concentration (mg/L) = (RF * Peak Area * Dilution Factor)(Spike Recovery)
To provide some measure of the quality (applicability) of the daily calibration factors (mean response factors), a relative standard deviation was calculated for each daily set of analyses by dividing the standard deviation of the individual response factors by the mean response factor. The relative standard deviation values derived from the two
calibrations did not exceed 7% for pentachloropyridine.

Instrument and Conditions for GC Analysis
GC: Agilent 6890N (EGC-0719) SN#: US10211081
Autosampler: Agilent 7683 SN#: US84603523 (tower)
Detector: Electron Capture Detector (ECD)
Capillary Column: 30 m x 0.32 mm, 0.25 mm film J&W Scientific HP-5 SN#: US2108471H
Temperatures:
Column Oven: 150oC isothermal for 5 minutes
Injection Port: 250oC
Detector: 275oC
Gases:
Carrier Gas: Nitrogen @ 20 psig headpressure
Make-up Gas: Nitrogen @ 20 mL/minute
Injection: 1-mL splitless; purge on at 0.25 minute
Data System: PerkinElmer’s TurboChromÔ System Perkins- Elmer, Inc., Wellesley, Massachusetts

Exposure Phase
The definitive test was conducted from 27 October to 31 October 2003. Four replicate test vessels were prepared per test concentration and control, each containing 100 mL of
test solution. Three replicates at each test concentration and the control group were inoculated with approximately 10,000 cells/mL. Inoculations were made after all the
replicate test vessels at each test concentration were poured. The fourth replicate at each test concentration and control group was not inoculated with algae to serve as a counting blank. These blanks were used to correct

the daily counts for the interference of the test material and to monitor pH and concentration of the test material without the algal biomass. The exposure phase was carried out aseptically under static conditions for four days (approximately 96 hours). The replicate test flasks were placed in a walk-in environmental chamber (Lab-Line Environmental Chamber, Lab-Line Inc., Melrose,
Illinois) according to a computer-generated randomization scheme. The replicate test flasks were randomized daily after sampling for cell counts. The incubator was thermostated at 24 ± 2°C with continuous light at approximately 8000 ± 1600 lux. Test conditions are presented in Table 2.

Physical Analysis
At test initiation, a pH measurement was taken from a sample of the bulk preparation of each test concentration and the control. At test termination, a final pH measurement was taken from a pooled sample of the replicates with algae at each test concentration and the
control and from each blank replicate. The incubator temperature was continuously monitored with a Fischer minimum/maximum thermometer probe placed in a
representative vessel within the incubator. The light intensity was monitored daily at positions corresponding to the test flasks in the incubator with a VWR Dual Display
Light Meter.

Density Determinations/Observations
Algal cell densities of the initial inoculum and test cultures were determined by electron particle counting using a Coulter Multisizer 3. Total cell counts were determined at approximately 24, 48, 72, and 96 hours. Cells were cumulatively counted at a lower threshold equivalent spherical diameter of approximately 2.6 µm to a higher threshold equivalent spherical diameter of approximately 8.7 µm. Three separate cell count readings were made
per replicate. The readings for the blank replicates were used to correct for background in daily calculations. Since there was no test material effect on the blanks, the mean of all the blanks was calculated and used to adjust the cell counts. The adjusted cell counts were converted to cells x 10000/mL (cell density) for statistical analysis and reporting.

In addition, at test termination morphological observations were done on a composited sample of the three inoculated replicates at each test concentration and control. The cells were observed under a microscope (Olympus® BHB-DO System Microscope; 20x or 40x objective lens; WF10x eyepiece; 1.25x Dual Observation Deck) using a Bright Line Hemacytometer Counting Chamber.

Statistical Analysis
The results (study endpoints) of the study were evaluated based on the nominal pentachloropyridine concentrations and are expressed in terms of algal growth (cells x 10,000/mL). The endpoints analyzed were cell density, growth rate (day-1), and biomass (area under the growth curve).
The control and the acetone control groups were compared using a t-test (a = 0.25) to determine whether the control groups could be pooled. The EC25 and EC50 values for cell density (those concentrations that limited cell density
to 25% and 50% of the test population, respectively, when compared to the control population) were determined by a least squares linear regression of cell density against the concentration at 72 and 96 hours for test concentrations where a clear dose relationship was observed.
The ErC50 value (the concentration that inhibited the growth rate to 50% of the test population, when compared to the control population) was empirically determined since
reduction in growth rate at both time points was less than 50%. The following formula was used to calculate growth rate:

$$mui\text{-}j = \frac{\ln Nj - \ln Ni}{tj\text{-}ti}$$

Where: mu = mean specific growth rate from moment i to j (days-1)
ln = natural logarithm
Ni = initial cell density at time i (cells/ml x 104)
Nj = cell density at time j
ti = the moment time for the start of the period
tj = the moment time for the end of the period

The EbC50 value (the concentration that inhibited biomass to 50% of the test population, when compared to the control population) was calculated by regression of the differences
in area under the growth curves for each dose group compared to the control against the log of the concentrations for 72 and 96 hours where a clear dose-response relationship was observed. Area under the growth curve was calculated using the following formula:

$$A = \frac{N1\text{-}N0}{2} \times t1 + \frac{N1+N2\text{-}2N0}{2} \times (t2\text{-}t1)$$

$$+ \frac{Nn\text{-}1+Nn\text{-}2N0}{2} \times (tn\text{-}tn\text{-}1)$$

Where: A = area under the growth curve
N0 = nominal number of cells/mL (x 104) at t0
N1 = measured number of cells/mL (x 104) at t1
Nn = measured number of cells/mL (x 104) at tn
t1 = time of first measurement after beginning of test
tn = time of nth measurement after beginning of test

Prior to evaluation of the no-observed-effect concentrations (NOECs), the data were tested for normality using the Shapiro-Wilk's Test and for homogeneity of variance using the Bartlett's Test. The 72- and 96- hour endpoints met the assumptions of homogeneity and normality, so the untransformed data for these endpoints were
evaluated using the Dunnett's test. Based on this, the 72- and 96- hour data for cell density, growth rate, and biomass (area under the growth curve) were analyzed using the analysis of variance and Dunnett's test (a = 0.05) to determine NOEC values.

Quality Assurance
The study conduct and data generated were reviewed according to the procedures of the Quality Assurance Unit of Toxicology & Environmental Research and Consulting, The
Dow Chemical Company, Midland, Michigan. Permanent records of all data generated during the course of this study, the protocol, any changes/revisions to the protocol, and a
copy of the final report were available for inspection by the Quality Assurance Unit.

Archival Statement
All data generated are archived at Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan.

Result : Chemical Analysis
The results obtained from the analyses of test solutions for pentachloropyridine are presented in Table 3. Results from the day 0

analysis yielded percent recovery of target
values for the bulk dose solutions ranging from 29.5 to 118%. The data exhibited a general trend in which the percent of recovery of target values decreased as the target concentrations increased, which is likely due to the limited solubility of pentachloropyridine in AAM. The measured pentachloropyridine concentrations were similar for the 0.500, 1.00, and 2.00 mg/L bulk dose solutions with values ranging from 0.437 to 0.613 mg/L, suggesting that a concentration plateau was achieved. Pentachloropyridine was not present at quantifiable concentrations in any of the day 4 test solutions (with or without algae). Mean measured concentrations for the exposure period were calculated for all dose levels by averaging the day 0 bulk dose solution
concentrations and the day 4 exposure solution concentrations. However, since the day 4 measured concentrations were all less than the lowest levels quantified (LLQ) of 0.0100 mg pentachloropyridine/L AAM for the controls, 0.125, 0.250, and 0.500 mg/L solutions and 0.101 mg pentachloropyridine/L AAM for the 1.00, 2.00, and 4.00 mg/L solutions, values of 0.005 and 0.05 mg/L (equivalent to ½ LLQ, respectively) were used in the calculations as a conservative estimate of day 4 exposure concentrations. The resulting overall mean measured concentrations ranged from 16.0 to 60.4 percent of target dose levels.

None of the analyses of the AAM or solvent controls exhibited a peak eluting at the retention time of pentachloropyridine at concentrations exceeding the lowest level quantified of 0.0100 mg/L AAM.

Method Precision and Solution Homogeneity
The variability associated with the analytical method, as well as solution homogeneity, was assessed on day 0 of the study. Four replicate samples were collected from day 0
bulk dose solutions at nominal concentrations of 0.125 and 4.00 mg pentachloropyridine/L AAM. Four repeated measurements (4 samples x 1 injection/sample) resulted in percent relative standard deviation (RSD) values of 2.84 and 7.99% in the low and high samples, respectively (data not shown).

Linearity
The GC/ECD instrumentation exhibited a linear response over the concentration range extending from ~0.1 to 6 µg pentachloropyridine/L iso-octane.

Lowest Level Quantified (LLQ)
Different LLQ values were used for the low concentration dose levels (controls, 0.125, 0.250, and 0.500 mg/L) and the high concentration dose levels (1.00, 2.00, and 4.00
mg/L) to account for the difference in sample dilution during preparation for analysis. The low concentration samples were diluted 100- fold resulting in an LLQ value of
0.0100 mg pentachloropyridine/L AAM while the high concentration samples were diluted 1010-fold to provide an LLQ value of 0.101 mg pentachloropyridine/L AAM.
The LLQ values were based upon the concentration of the lowest standard analyzed times the dilution factor.

Test Conditions
Temperature (°C), light intensity (lux), and pH data ranges observed during the four-dayexposure phase are summarized in Table 5. Temperatures during the exposure period
ranged from 24.4 - 24.6°C. The mean (± standard deviation) light intensity was 7346 ± 445 lux, with a range of 6410 - 8200 lux. The pH values ranged 6.8 to 7.0 at test
initiation, from 8.9 to 9.6 in pooled replicates with algae at test termination,

and from 6.6 to 7.1 in blank replicates without algae at test termination.

Biological Data
All biological results are expressed in terms of nominal concentrations of pentachloropyridine. There was a clear dose-related inhibition in cell density over all test levels. However, analytical recoveries from the Day 0 test solutions indicated no dose related increase in residues above the 0.500 mg/L nominal test level. The samples taken for residue determinations were centrifuged prior to extraction, which most likely removed undissolved test material from the test media (see Test Material section). Thisindicates that the solubility of pentachloropyridine in AAM was approximately 0.500 mg/L. Since there was a dose related biological response, it was decided to statistically analyze the data using the nominal concentrations. This is the only way a meaningful dose-response endpoint (i.e., EC50) could be calculated.

Mean cell densities at 72 hours were 201.0, 152.6, 174.1, 166.2, 140.1, 138.4, 76.76, and 23.99 x 104 cells/mL for the control, acetone control, 0.125, 0.250, 0.500, 1.00, 2.00, and 4.00 mg/L test levels, respectively. The t-test analysis indicated that the control data should not be pooled ($p < 0.25$), so the statistical comparisons for this endpoint were made to the acetone control. Response relative to the acetone controls ranged from 14% stimulation to 84% inhibition of growth. The 72-hour calculated EC25 and EC50 values (95% confidence intervals) for cell density were 1.26 (< 0.125-3.15) and 2.39 (0.474-> 4.00) mg/L, respectively. Based on the Dunnett's test, the 72-hour cell density was significantly less than the acetone controls at the 4.00 mg/L test level; therefore, the 72-hour NOEC value for cell density was determined to be 2.00 mg/L. Mean cell densities at 96 hours were 457.5, 409.1, 449.9, 425.7, 379.5, 372.0, 241.4, and 108.6 x 104 cells/mL for the control, acetone control, 0.125, 0.250, 0.500, 1.00, 2.00, and 4.00 mg/L test levels, respectively. The t-test analysis indicated that the control data should not be pooled ($p < 0.25$), so the statistical comparisons for this endpoint were made to the acetone control. Response relative to the acetone controls ranged from 10% stimulation to 73% inhibition of growth. The 96-hour calculated EC25 and EC50 values (95% confidence intervals) for cell density were 1.44 (0.107-2.77) and 2.74 (1.38-> 4.00) mg/L, respectively. Based on the Dunnett's test, the 96-hour cell density was significantly less than the controls at test levels >= 2.00 mg/L; therefore, the 96-hour NOEC value for cell density was determined to be 1.00 mg/L.

Mean specific growth rates at 72 hours were 1.765, 1.672, 1.710, 1.691, 1.627, 1.640, 1.445, and 1.033 day-1 for the control, acetone control, 0.125, 0.250, 0.500, 1.00, 2.00, and 4.00 mg/L test levels, respectively. The t-test analysis indicated that the control data should not be pooled ($p < 0.25$), so the statistical comparisons for this endpoint were made to the acetone control. Response relative to the acetone controls ranged from 2% stimulation to 38% inhibition of growth rate. The empirically determined 72-hour ErC50 value for specific growth rate was > 4.00 mg/L, the highest level tested. Based on the Dunnett's test, the 72-hour specific growth rate was significantly less than the controls attest levels >= 2.00 mg/L; therefore, the 72-hour NOEC value for specific growth rate was determined to be 1.00 mg/L.

Mean specific growth rates at 96 hours were 1.531, 1.502, 1.526, 1.513, 1.483, 1.480,1.367, and 1.149 day-1 for the control, acetone control, 0.125, 0.250, 0.500, 1.00, 2.00, and 4.00 mg/L test levels, respectively. The t-test analysis indicated that

the control data should not be pooled ($p < 0.25$), so the statistical comparisons for this endpoint were made to the acetone control. Response relative to the acetone controls ranged from 2% stimulation to 24% inhibition of growth rate. The empirically determined 96-hour ErC50 value for specific growth rate was > 4.00 mg/L, the highest level tested. Based on the
Dunnett’s test, the 96-hour specific growth rate was significantly less than the controls at test levels >= 2.00 mg/L; therefore, the 96-hour NOEC value for specific growth rate was determined to be 1.00 mg/L.

Mean biomass area values at 72 hours were 3656, 2948, 3212, 3078, 2537, 2342, 1320, and 383 day-1 for the control, acetone control, 0.125, 0.250, 0.500, 1.00, 2.00, and 4.00 mg/L test levels, respectively. The t-test analysis indicated that the control data should not be pooled ($p < 0.25$), so the statistical comparisons for this endpoint were made to the acetone control. Response relative to the acetone controls ranged from 9% stimulation to 87%
inhibition of biomass. The 72-hour calculated EbC50 value (95% confidence intervals) for biomass was 1.66 (0.871-3.15) mg/L. Based on the Dunnett’s test, the 72-hour biomass was significantly less than the controls at test levels >= 2.00 mg/L; therefore, the 72-hour
NOEC value for biomass was determined to be 1.00 mg/L.
Mean biomass area values at 96 hours were 11533, 9665, 10676, 10157, 8749, 8444, 5113, and 1951 day-1 for the control, acetone control, 0.125, 0.250, 0.500, 1.00, 2.00, and 4.00 mg/L test levels, respectively. The t-test analysis indicated that the control data should not be pooled ($p < 0.25$), so the statistical comparisons for this endpoint were made to the acetone control. Response relative to the acetone controls ranged from 10% stimulation to 80% inhibition of biomass. The 96-hour calculated EbC50 value (95% confidence intervals) for biomass was 2.03 (0.937-> 4.00) mg/L. Based on the Dunnett’s test, the 96-hour biomass was significantly less than the controls at test levels >= 2.00 mg/L;
therefore, the 96-hour NOEC value for biomass was determined to be 1.00 mg/L.

Microscopic evaluation of cells at each test concentration and the control revealed no abnormal observations at any test level.

Table 1. Typical Culturing Conditions
Organism: Pseudokirchneriella subcapitata (formerly know as Selenastrum capricornutum), a freshwater green alga
Temperature: 24 ± 2°C
Light (lux): 4300 ± 650
Photoperiod: Continuous
Medium: Algal assay medium (AAM) designated for the EPA algal assay bottle test
pH: Range: approximately 7.0-7.5
Culture Conditions: Axenic
Culture Volume: 200 mL
Culture Vessel: 500-mL Erlenmeyer flask
Culture Vessel Cap: Shimadzu closure

Table 2. Typical Testing Conditions
Habitat: Environmental Growth Chamber
Temperature °C: 24 ± 2°C
Light (lux): 8000 ± 1600
Photoperiod: Continuous
Agitation: Continuous (100 rpm)
Medium: Algal Assay Medium
Test Conditions: Axenic

Test Vessel 250-mL Erlenmeyer flask
Test Volume 100 mL
Replicates/Concentration 4 (3 with algae, 1 without algae)
Replicates/Control 4 (3 with algae, 1 without algae)
Length of Exposure 4 days (approximately 96 hours)
Initial Cell Density:
Exposure Phase ~ 10,000 cells/mL
Measurements:
Lights Daily
Temperature Continuous
pH Initiation and Termination
(with and without algae)
Observations:
Hours 24, 48, 72, and 96 Total cell counts/mL (microscopic evaluation of cell morphology at 96 hours)
Endpoints: Cell Density (cells/mL), Growth Rate, and Biomass (area under the growth curve)

Source : The Dow Chemical Company, Midland, MI.

Conclusion : The purpose of this study was to assess the effects of pentachloropyridine on the growth of Pseudokirchneriella subcapitata (formerly known as Selenastrum capricornutum), a freshwater green alga. The freshwater alga was exposed to six nominal test concentrations of 0.125, 0.250, 0.500, 1.00, 2.00, and 4.00 mg/L mg pentachloropyridine/L of algal assay medium, plus a medium control and an acetone control, over a 96-hour period. Recoveries on day 0 ranged from 29.5 to 118% of nominal. The wide range in recoveries was most
likely due to decreasing solubility as nominal concentrations increased, combined with centrifugation of the analytical samples prior to extraction. Measured concentrations did not increase in a dose dependent fashion at nominal test levels above 0.500 mg/L. Based on
these recoveries, the solubility of pentachloropyridine in algal assay medium was determined to be approximately 0.500 mg/L. Analytical residues at test termination (day 4)
were less than the LLQ at all test concentrations. Even though measured test levels did not increase in dose dependent fashion above 0.500 mg/L (nominal), there was a clear dose response in biological effect. This indicated that the measured concentrations at the higher test levels were not reflective of the actual exposure (i.e., undissolved test material was present that was not measured due to centrifugation). Based on this, statistical analysis of the biological data was conducted using the nominal test concentrations.
The 72-hour results, based on nominal pentachloropyridine concentrations, were as follows:
· The 72-hour EC25, EC50, and NOEC values for cell density were 1.26, 2.39, and
2.00 mg/L, respectively.
· The 72-hour ErC50 and NOEC values for growth rate (day-1) were > 4.00 and 1.00
mg/L, respectively.
· The 72-hour EbC50 and NOEC values for biomass (area under the growth curve)
were 1.66 and 1.00 mg/L, respectively.
The 96-hour results, based on nominal pentachloropyridine concentrations, were as
follows:
· The 96-hour EC25, EC50, and NOEC values for cell density were 1.44, 2.74, and
1.00 mg/L, respectively.
· The 96-hour ErC50 and NOEC values for growth rate (day-1) were > 4.00 and 1.00
mg/L, respectively.
· The 96-hour EbC50 and NOEC values for biomass (area under the

growth curve)
were 2.03 and 1.00 mg/L, respectively.

Reliability : (1) valid without restriction
21.09.2004 (13)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : = 435 mg/kg bw
Species : rat
Strain : Fischer 344
Sex : male
Number of animals : 12
Vehicle : other: corn oil
Doses :
Method : other
Year : 1987
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Young adult male rats were fasted overnight. They were administered the material as a solution in corn oil at a dose volume of 10 ml/kg bw at dose levels of 100, 250, 500, or 750 mg/kg bw. Animals were observed closely for two weeks, then submitted for pathological examination. All animals which died prior to scheduled necropsy were also submitted for pathological examination. Body weights were recorded on the day of treatment (Study Day 0), and Study Days 1, 8, and 15.

Result : Acute oral toxicity was characterized as moderate. The acute oral LD50 for male rats was approximately 435 mg/kg, when calculated using the moving average method.

Dose (mg/kg)	Number Treated	Number Dead
100	3	0
250	3	0
500	3	2
750	3	3

In-life signs of toxicity were observed only in rats receiving 500 or 750 mg/kg, and included lethargy, tremors/muscle spasms, lacrimation, palpebral closure, and death on the day of treatment. No clinical evidence of treatment-related effects were seen at 100 or 250 mg/kg. All surviving rats gained weight over the 2-week observation period.

Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
Study conducted in accordance with generally accepted scientific principles.
GLP not compulsory at time study was performed.

05.06.2002 (14)

Type : LD50
Value : = 126 - 1000 mg/kg bw
Species : rat
Strain : no data
Sex : female
Number of animals : 3
Vehicle : other: rodent chow
Doses :
Method : other
Year : 1963
GLP : no

Test substance : as prescribed by 1.1 - 1.4

Source : The Dow Chemical Company, Midland, MI.
Reliability : (2) valid with restrictions
05.06.2002 (15)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species : rabbit
Concentration : undiluted
Exposure : Occlusive
Exposure time : 24 hour(s)
Number of animals : 1
Vehicle :
PDII :
Result : moderately irritating
Classification :
Method : other
Year : 1965
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Neat Material: A male rabbit was prepared by shaving the hair from the entire abdomen with a straight razor and barber soap. The animal was then rested for several days to allow any abrasions to heal completely and to be sure skin was suitable for use. Two sites on the abdomen were used for applications: one intact, the other cross-hatched with a sharp hypodermic needle to penetrate the stratum corneum but not to produce more than a trace of bleeding. Ten applications were made to the intact abdominal site over a period of 14 days. Three consecutive daily applications were made to the abraded site. Both abdominal sites were covered with 1X1 cotton pads and held place with a single cotton cloth taped to remaining body hair. Applications were discontinued upon production of a substantial skin burn, or if the animal died.

10% Dilution in Dowanol* DPM: A male rabbit was prepared by shaving the hair from the entire abdomen with a straight razor and barber soap. The animal was then rested for several days to allow any abrasions to heal completely and to be sure skin was suitable for use. Ten applications (unoccluded) were made to the ear over a period of 14 days. Two sites on the abdomen were used for applications: one intact, the other cross-hatched with a sharp hypodermic needle to penetrate the stratum corneum but not to produce more than a trace of bleeding. Ten applications were made to the intact abdominal site over a period of 14 days. Three consecutive daily applications were made to the abraded site. Both abdominal sites were covered with 1X1 cotton pads and held place with a single cotton cloth taped to remaining body hair. Applications were discontinued upon production of a substantial skin burn, or if the animal died.

Result : Neat Material: At the intact abdominal site, slight to moderate hyperemia and slight edema was observed during the first week of application. Slight necrosis appeared after the 5th application. All signs of irritation resolved within 21 days. Similar results were seen at the abraded abdominal site, with the exception that necrosis was first observed after the 4th application.

10% Dilution in Dowanol* DPM: The site at the rabbit ear had no signs of irritation. Both the intact and abraded abdominal sites had slight to moderate hyperemia and edema appear within the first week. All signs of irritation resolved within 21 days.

Source : The Dow Chemical Company, Midland, MI.

05.06.2002 (16)

5.2.2 EYE IRRITATION

Species : rabbit
Concentration : undiluted
Dose : .1 ml
Exposure time : 24 hour(s)
Comment :
Number of animals : 1
Vehicle :
Result : not irritating
Classification : not irritating
Method : other
Year : 1965
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Both eyes of a white rabbit were stained with 5% fluorescein dye and examined for evidence of injury or alterations. The rabbit was then allowed to rest for 24 hours before test.

Two drops of the material were introduced into the right eye. The eye was washed within 30 seconds for 2 minutes in a flowing stream of tepid water. Two drops of material were introduced in a similar fashion to the left eye, but this eye was left unwashed.

Immmediately after instillation into each eye, the rabbit was examined for signs of discomfort. Within 2-3 minutes after the unwashed eye was treated, each eye was observed for conjunctival and corneal response. Similar observations were made on both eyes at 1 hour, 24 hours, 48 hours, and 6-8 days post-treatment. Examinations were conducted both with and without fluorescein dye.

Result : In both washed and unwashed eyes, the material caused very slight discomfort and very slight conjunctival irritation which resolved within 1 hour.

Source : The Dow Chemical Company, Midland, MI.

05.06.2002 (16)

5.3 SENSITIZATION

Type : Split adjuvant test
Species : guinea pig
Concentration : 1st: Induction 5 % intracutaneous
2nd: Challenge 5 % open epicutaneous
3rd:
Number of animals : 8

Vehicle	:	other: Dowanol* DPM/Tween* 80, 9/1
Result	:	sensitizing
Classification	:	
Method	:	other
Year	:	1965
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	The Dow Chemical Company, Midland, MI.

05.06.2002 (16)

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm.	:	continuous
Post exposure period	:	none
Doses	:	0, 0.3, 1, 3, 10, 30 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL	:	= 10 mg/kg bw
LOAEL	:	= 30 mg/kg bw
Method	:	other
Year	:	1968
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Groups of 10-15 45-day old rats/sex/dose group were treated with 0, 0.3, 1, 3, 10, or 30 mg/kg/day via diet. Rats were randomly assigned to treatment groups. Vehicle for the test material and feed for the controls was Purina ground rodent chow.

Diets designed to deliver the nominal dose were mixed weekly on the basis of rat body weight and feed consumption. Body weights and feed consumption were collected once/week for the duration of the study. All animals were observed frequently for clinical signs of toxicity.

Blood samples were collected from 5 rats/sex/dose from the 0, 10, and 30 mg/kg/day levels via orbital sinus puncture during weeks 3 and 12, and at termination. Hematological parameters examined included Hgb, crit, RBC, WBC, and differential counts. Blood urea nitrogen determinations were run on 10 rats/sex/dose at termination, and SGPT determinations were run for 5 rats/sex/dose at 0 and 30 mg/kg/day levels on days 1, 3, 7, 14, 30, and termination (10 rats/sex/dose).

A complete necropsy examination, including both gross pathological and histopathological examinations, was conducted on a standard set of tissues, including reproductive organs. Weights were collected for lungs, heart, liver, kidneys, spleen, testes, and brain.

In an effort to clarify testicular findings among dosed rats, additional studies were undertaken.

Repeated intubation: Groups of 10 male rats/dose were given 0, 62.5, 125, or 250 mg/kg/day via gavage 5 days/week for 2 weeks. Rats were necropsied 3 and 18 days after the last dose Body weights and testicular weights were recorded, and testes, prostate, seminal vesicles, coagulating gland, and epididymis were examined for microscopic lesions. SGPT determinations were conducted at necropsy.

Dietary: Groups of 30 male rats were given diets at dose levels of 0, 62.5, 125, or 250 mg/kg/day. 5 rats/dose were necropsied on test days 49, 119, 175, and 242. Body weights and testicular weights were recorded, and testes, prostate, seminal vesicles, coagulating gland, and epididymis were examined for microscopic lesions. Livers were also examined on rats killed on days 175 and 242. SGPT determinations were conducted at necropsy.

Result : There were no treatment-related morphological changes observed at any level in females.

Male rats given 30 mg/kg/day had increased relative liver and kidney weights and mild focal hyaline droplet degeneration of the convoluted tubules of the renal cortex. No histological changes were observed in livers.

Testicular tubal atrophy of varying degrees was observed at all dose levels in the male rats. Not all animals within a dose level were affected, and severity was not dose-related.

In the follow-up studies, no treatment-related differences were observed for final body weight, testicular weight, gross pathology and histopathology. There was a marked degeneration of SGPT values at all dose levels. In the repeated intubation experiment, values were moderately depressed 3 days after final dosing, but returned to normal by the 18 day kill. In the dietary experiment, SGPT values were severely depressed at 49 and 119 days. Values at 175 and 242 days improved, but were still markedly lower than controls. Testicular effects observed in the earlier study could not be replicated, even at these much higher dose levels.

Histopathology Peer Review of Two Pentachloropyridine 90-Day Dietary Feeding Studies in Rats:

In the first study ten adult rats per sex per dose level were provided dose concentrations of 0 (controls), 0.3, 1, 3, 10 or 30 mg pentachloropyridine (PCP) per kilogram body weight per day in the feed for 90 days. The histopathologic peer review of this study consisted of microscopic evaluation of both testes from all male rats at all dose levels. The peer review was conducted by a Diplomate of the American College of Veterinary Pathologists. Results of the peer review histopathologic evaluation showed that there were no treatment-related testicular effects. This was in agreement with the final conclusions of the original pathologist. There were comparable numbers of rats at all dose levels, including the control group, with very slight or slight degeneration of testicular seminiferous tubules. The quality of the microscopic slides from this study was less than optimal, with artifacts of poor fixation or processing methods, and evidence of rough physical handling of some testicular specimens. Some of the histopathologic diagnoses made by the original pathologist were determined to be reflective of artifactual changes, based on examination by the peer review pathologist. The diagnoses that were attributed to poor fixation or rough tissue handling consisted of interstitial edema, vacuoles in seminiferous tubules, and the presence of primary or secondary spermatocytes in the lumens of seminiferous tubules.

In the second study groups of 30 male rats per dose level were provided dose concentrations of 0 (controls) 62.5, 125 or 250 mg PCP per kilogram body weight per day in the feed. Five rats per dose group were necropsied after 49, 119, 175 and 242 days on the diet. The histopathologic peer review of this study consisted of microscopic evaluation of both testes from all male rats at all dose levels. The peer review was conducted by a Diplomate of the American College of Veterinary Pathologists. Results of the peer review histopathologic evaluation showed that there were no treatment-related testicular effects. This was in agreement with the original pathologist. As with the previous 90-day study, there were comparable numbers of rats at all dose levels, including the control group, with very slight or slight degeneration of testicular seminiferous tubules. The quality of microscopic slides in the second study was optimal, with no significant artifacts related to fixation, processing, or tissue handling.

Source : The Dow Chemical Company, Midland, MI.
Reliability : (2) valid with restrictions
26.09.2003 (17)

Type :
Species : rat
Sex : no data
Strain : other: Alderly Park
Route of admin. : inhalation
Exposure period : 6 hours
Frequency of treatm. : 16 exposures
Post exposure period : none
Doses : saturated vapor; ~1 ppm (0.01 mg/L)
Control group : no data specified
NOAEL : = 1 ppm
Method : other
Year : 1970
GLP : no
Test substance : no data

Result : No rats died, no toxic signs were observed, and no organs were affected at necropsy.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (2) valid with restrictions
05.06.2002 (18)

5.5 GENETIC TOXICITY ‘IN VITRO‘

Type : Bacterial reverse mutation assay
System of testing : Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and Echerichia coli strain WP2uvrA
Test concentration : 0.33-3333 (activation) and 3.3-3333 microg/plate (no activation)
Cycotoxic concentr. : 1000 microg/plate
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 471
Year : 2003
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The Salmonella-E. coli mammalian-microsome bacterial reverse mutation assay is used to evaluate the mutagenic potential of test agents in bacteria with and without
mammalian-microsome activation (Ames et al., 1975; Maron and Ames, 1983; Green and Muriel, 1976). The strains of Salmonella typhimurium used in this assay (TA98, TA100,
TA1535, TA1537) are histidine auxotrophs while E. coli WP2uvrA is a tryptophan auxotroph, by virtue of conditionally lethal mutations in the appropriate operons. When these histidine (his-) or tryptophan (trp-) dependent cells are exposed to the test article and grown under selective conditions (minimal media with a trace amount of histidine or tryptophan), only those cells that revert to histidine (his+) or tryptophan (trp+) independence are able to form colonies. The trace amount of histidine or

tryptophan in the media allows all the plated bacteria to undergo a few cell divisions that are essential for mutagenesis to be fully expressed. The (his+) or (trp+) revertants are readily discernable as colonies against the limited background growth of the his- or trp- cells.

In addition to a mutation in the histidine operon, the Salmonella typhimurium tester strains contain additional mutations that enhance their sensitivity to some mutagenic compounds. A mutation of the uvrB gene results in a deficient DNA excision repair system that greatly enhances the sensitivity of these strains to some mutagens. Since the uvrB deletion extends through the bio gene, the tester strains also require the vitamin biotin for growth.

These Salmonella typhimurium tester strains also contain the rfa wall mutation that results in the loss of one of the enzymes responsible for the synthesis of part of the
lipopolysaccharide (LPS) barrier that forms the surface of the bacterial cell wall. The resulting cell wall deficiency increases permeability to certain classes of chemicals such as those containing large ring systems (e.g., benzo[a]pyrene) that would otherwise be excluded by a normal intact cell wall. Strain TA98 and TA100 also contain the pKM101 plasmid, which further increases the sensitivity of this strain to some mutagens. The mechanism by which this plasmid increases sensitivity to mutagens has been suggested to be a consequence of its modification of an existing bacterial DNA-repair polymerase complex involved in the mismatch-repair process. The tester strains TA98 and TA1537 are reverted from histidine dependence (auxotrophy) to histidine independence (prototrophy) by frameshift mutagens, while TA100 and TA1535 and the E. coli strain WP2uvrA are reverted by base-pair substitution. The utilization of a mammalian microsomal enzyme preparation
(S-9 mix) also allows for detection of potentially mutagenic metabolites of the test material.

The specific genotypes of the strains are shown in Text Table 1.
TEXT TABLE 1. TESTER STRAIN GENOTYPES

Tester Strain	his/trp Mutation	Additional Mutations Repair	LPS	Plasmid pKM101	Mutation Type Detection
TA98	hisD3052	uvrB	rfa	+	Frameshift
TA100	hisG46	uvrB	rfa	+	Base-pair Substitution
TA1535	hisG46	uvrB	rfa	-	Base-pair Substitution
TA1537	hisC3076	uvrB	rfa	-	Frameshift
WP2uvrA	trp	uvrA	-	-	Base-pair Substitution

Bacterial Tester Strains
The Salmonella typhimurium and E. coli tester strains used in this study (TA98, TA100, TA1535, TA1537 and E.coli WP2uvrA) were acquired from a vendor (Moltox Inc., Boone, North Carolina), who prepared them from master cultures originally obtained from the laboratory of Dr. Bruce N. Ames (Maron and Ames, 1983) and the National Collections of Industrial and Marine Bacteria (Green and Muriel, 1976). Their characteristics are detailed in the Text Table 1 above. Frozen permanent stocks were prepared by growing fresh overnight cultures, adding DMSO (0.09 mL/mL of culture) and freezing appropriately vialed aliquots. Frozen permanent stocks of the tester strains were stored in liquid nitrogen vapor or at least at

£ -70°C.

Tester Strain Media
All tester strain media and experimental reagents were acquired from (Moltox Inc., Boone, North Carolina). The broth used to grow overnight cultures of the tester strains
was Vogel-Bonner salt solution (Vogel and Bonner, 1956) supplemented with 2.5% (w/v) Oxoid Nutrient Broth #2 (dry powder). Bottom agar (25 mL per 15 x 100 mm petri dish)
was Vogel-Bonner minimal medium E (Vogel and Bonner, 1956) supplemented with 1.5% (w/v) agar and 0.2% (w/v) glucose. Top (overlay) agar was prepared with 0.7% agar (w/v) and 0.5% NaCl (w/v) supplemented with 10 mL of 0.5 mM histidine/biotin solution per 100 mL agar for selection of histidine revertants or 0.5 mM tryptophan solution per 100 mL agar for selection of tryptophan revertants. For an agar overlay, 2.0 mL of the supplemented top agar was used.

Chemicals and S-9
Glucose-6-phosphate, nicotine adenine dinucleotide phosphate (NADP), dimethylsulfoxide (DMSO), 2-nitrofluorene, sodium azide, ICR-191, 4-nitroquinolone-Noxide, benzo(a)pyrene and 2-aminoanthracene were obtained from Sigma Chemical
Company, St. Louis, Missouri. The S-9 activation system consisted of an NADPH regeneration system plus the S-9 fraction of rat liver homogenate. The S-9 fraction of rat
liver homogenates prepared from Aroclor®-1254-induced male Sprague-Dawley rats (500 mg/kg, i.p.) was purchased from Moltox Inc. and stored at –100oC or below. Immediately prior to use, the S-9 was thawed and mixed with a cofactor pool to contain 10% S-9 homogenate, 5 mM glucose-6-phosphate, 4 mM b-nicotinamide-adenine
dinucleotide phosphate, 8 mM MgCl2 and 33 mM KCl in a 200 mM phosphate buffer at pH 7.4. This mixture is referred to as S-9 mix. In the absence of S-9, the non-activation mix was 200 mM phosphate buffer at pH 7.4. All other constituents were reagent grade or better.

Assay Control Chemicals
Vehicle controls were plated for all strains in the absence and presence of S-9 mix as appropriate and constituted the solvent (0.2 M phosphate buffer) used for the test material.

TEXT TABLE 2. POSITIVE CONTROLS FOR THE BACTERIAL MUTAGENICITY ASSAY

Strain	S-9 Mix	Positive Control	Concentration Per Plate
TA98	-	2-NITROFLUORENE	5 microg
TA100	-	SODIUM AZIDE	2 microg
TA1535	-	SODIUM AZIDE	2 microg
TA1537	-	ICR-191	2 microg
WP2uvrA (E. coli)	-	4-NITROQUINOLINE -N-OXIDE	0.4 microg
TA98	+	BENZO(A)PYRENE	2.5 microg
TA100	+	2-AMINOANTHRACENE	2.5 microg
TA1535	+	2-AMINOANTHRACENE	2.5 microg
TA1537	+	2-AMINOANTHRACENE	2.5 microg
WP2uvrA (E. coli)	+	2-AMINOANTHRACENE	25 microg

The most concentrated test article dilution and the buffers and S-9 mixes were checked for sterility by being mixed with top agar, poured onto

nutrient agar and incubated along with the other treated test plates. Text Table 2 above outlines the positive control chemicals used in the study. The positive controls were of reagent grade or better. The concentrations of positive controls were based on concentration response data from this laboratory. The
selected concentrations of the test material in the treatment solutions used for the main assay were verified by the Analytical Chemistry Laboratory, Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan using high performance liquid chromatography with ultraviolet detection (HPLC/UV).

Confirmation of Tester Strain Genotype
Tester strain cultures were checked for the following genetic markers concurrent with their use in the assay. The presence of the rfa wall mutation was confirmed by
demonstration of the sensitivity of the cultures to crystal violet. The presence of the pKM101 plasmid was confirmed for cultures of tester strain TA98 and TA100 by
demonstration of resistance to ampicillin.

Culturing and Harvest
Overnight cultures for each strain, for use in all testing procedures, were inoculated by transferring a colony from the appropriate master plate to a flask containing 20 ml of
culture medium. Inoculated flasks were placed in a shaker-incubator at 100 RPM 37 ± 2°C overnight and harvested once a predetermined density was reached according to spectrophotometric turbidity measurements at 650 nm. The cultures were adjusted to a density of at least 0.3 x 109 cells per mL and held at 5 ± 3°C until used in the assay.

Preliminary Mutagenicity Assay
Selection of dose levels for the main mutagenicity assay was based upon the toxicity and precipitation profile of the test article assessed in a preliminary assay. The tester strains were exposed to the test article via the pre-incubation modification of the Ames test described by Maron and Ames (1983). In the pre-incubation methodology, the tester strain and the test article were pre-incubated on an orbital shaker at 37oC for approximately 20 minutes prior to the addition of molten agar. The test material was
evaluated up to a concentration of 5000 mg/plate. The concentrations selected under these conditions were 5000, 3333, 1000, 333, 100, 33, 10, 3.3, and 1 mg/plate in the
presence and absence of S-9.

For the assay with activation, the bacteria (0.1 ml), test article (0.05 ml of the appropriately diluted test material or solvent), and the S-9 mix (0.5 ml) were placed into
sterile tubes, pre-incubated on an gyratory shaker (100 rpm) at 37°C for approximately 20 minutes prior to the addition of 2 ml of molten top agar (supplemented with trace amounts of histidine and biotin or tryptophan). The mixture was then poured onto minimal glucose agar plates. For the non-activation assay, S-9 mix was omitted and
replaced by 0.5 ml of 0.2M phosphate buffer, pH 7.4. The plates were then incubated for approximately 52 ± 4 hour in an incubator at 37°C. This preliminary mutagenicity assay
was conducted by exposing all strains to negative controls (three plates) and positive controls (two plates) and to nine concentrations of test article (two plates/dose), in both the presence and absence of S-9 activation.

Mutagenicity Assay
In selecting concentration levels for the mutagenicity assay, the following guidelines were employed. Concentrations were selected based on the

preliminary mutagenicity assay such that precipitate did not interfere with the counting of colonies. The highest concentration for the mutagenicity assay was also selected to give some indication of toxicity without exceeding 5 mg/plate.

Pentachloropyridine was tested at 6-8 concentration levels along with appropriate negative and positive controls with all tester strains (TA98, TA100, TA1535, TA1537, and WP2uvrA), with and without S-9 activation. All concentration levels of test article, negative controls, and positive controls were plated in triplicate.

Plate Evaluation
Prior to scoring the assay plates, all tester strain cultures were checked for the appropriate genetic markers. The condition of the bacterial background lawn was evaluated for evidence of cytotoxicity and test article precipitate. Evidence of cytotoxicity was scored relative to the vehicle control and recorded along with the revertant counts for that concentration. Revertant colonies were counted either by an Artek automated colony counter or by hand when revertant colony numbers were low. Plates that were not evaluated immediately following the incubation period were held at 5 ± 3°C until such time that colony counting and bacterial background lawn evaluation took place, but not more than two weeks.

Evaluation Criteria
To demonstrate the presence of the rfa mutation, all Salmonella typhimurium tester strain cultures must exhibit sensitivity to crystal violet. To demonstrate the presence of the pKM101 plasmid R-factor, the tester strain culture of TA98 and TA100 must exhibit resistance to ampicillin as described above.

Positive and negative controls were run concurrently with the test chemical, and appropriate responses for these controls were prerequisite for evaluating the response of
the bacteria to the test chemical.

A minimum of three non-toxic dose levels was required to evaluate assay data. For a test article to be judged positive for TA98, TA1535, TA1537, and E. coli WP2uvrA, a
concentration-related increase in mean revertants must be equal to or greater than 3.0-times the mean negative control value (vehicle). Similarly, for strain TA100, data
sets were judged positive if the concentration-related increase in mean revertants is equal to or greater than 2.0-times the mean negative control value (vehicle).

Result : The mutagenicity of pentachloropyridine was evaluated using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and Echerichia coli strain WP2uvrA in the presence and absence of a metabolic activation system (S-9).

Preliminary Assay
A preliminary assay (A1, Tables 1 and 2) was conducted on all tester strains (two plates per treatment) in both the presence and absence of metabolic activation (S-9 mix) at
concentrations ranging from 1-5000 mg/plate. Precipitate was observed at 3333 and 5000 mg both in the presence and in the absence of S-9 in all strains. Furthermore,
precipitation and cytotoxicity was also observed at 1000 mg/plate and above for strains TA98, TA100, and TA1537 in the absence of S-9 only. No evidence of increases in
mutant counts required to satisfy the conditions for a positive response were observed in any of the tester strains.

Mutagenicity Assay
The assay was conducted in all five tester strains, with 6-8 different treatments of pentachloropyridine in both the presence and absence of S-9 metabolic activation at
concentrations ranging from 0.33-3333 and 3.3-3333 mg/plate in the presence and absence of S-9 metabolic activation, respectively.

This mutagenicity assay (Assay B1) was repeated for strains TA100 and TA1537 under non-activation conditions because of a failure of the positive control for TA100, and a greater than expected cytotoxicity for TA1537, which did not allow for enough non-cytotoxic concentration levels to be evaluated for this strain. The remaining strain and activation conditions did not exhibit increases in revertants/plate required to fulfill the criteria for a positive response. The concentrations of test material in the dosing solutions were analytically confirmed to be between 77-101% of those targeted.

The mutagenicity assay (Assay B1) was repeated for strains TA100 and TA1537 under non-activation conditions. The repeat mutagenicity assay (Assay B2) for these strains (TA100 and TA1537) were performed at nine concentrations
from 0.033-3333 mg/plate in the absence of S-9. While evidence of cytotoxicity and precipitation was observed at the three highest concentrations, there were no positive
increases in mutant colonies in either strain. All criteria for a valid assay were met. The concentrations of test material in the dosing solutions were analytically confirmed to be between 102-124% with the exception of the two lower concentrations near the limit of detection, which were 135 and 159% of the target.

Source : The Dow Chemical Company, Midland, MI.
Conclusion : Results of this study indicate that pentachloropyridine did not induce an increase in revertants/plate over the negative control in any tester strain either in the presence and absence of S-9, required to satisfy the criteria for a positive response. Hence, pentachloropyridine is concluded to be negative in the bacterial reverse mutation assay under the conditions used in this study.
Reliability : (1) valid without restriction
22.09.2004 (7)

Type : Chromosomal aberration test
System of testing : Rat lymphocytes
Test concentration : 3.8, 15 and 30 (no activation); 7.5, 30 and 60 (activation) microg/ml
Cycotoxic concentr. : 60 µg/ml
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 473
Year : 2003
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Animal Husbandry
Blood samples were collected from male Sprague-Dawley rats (outbred Crl: CD BR strain purchased from Charles River, Kingston, New York), aged approximately 10 weeks. Upon arrival at the laboratory1, each animal was evaluated by a laboratory veterinarian to determine general health status and acceptability for study purposes. The rats were entered into an animal log, given unique numbers, and ear tagged with their numbers. The rats were allowed to acclimate for at least seven days prior to the start of the study.

Housing

Animals were housed one per cage in suspended stainless steel cages in rooms designed to maintain adequate conditions (temperature, humidity, and photocycle). The relative humidity was maintained within a range of 40-70%. A 12-hour light/dark photocycle was maintained for all animal rooms with lights on at 6:00 a.m. and off at 6:00 p.m. Room air was exchanged at 12-15 times/hour and the room temperature was maintained at 22 ± 1 (with a maximum range of ± 3 °C). Cages had wire-mesh floors and were
suspended above catch pans. Cages contained a stainless steel feeder and a pressure activated nipple-type watering system.

Identification
Animals were identified with each animal receiving an unique alphanumeric metal ear tag.

Feed and Water
Animals were provided LabDietâ Certified Rodent Diet #5002 (PMI Nutrition International, St. Louis, Missouri) in pelleted form. Feed and municipal water was provided ad libitum. Analysis of the feed was performed by PMI Nutrition International to confirm the diet provided adequate nutrition and to quantify the levels of selected
contaminants. Drinking water obtained from the municipal water source was periodically analyzed for chemical parameters and biological contaminants by the municipal water department. In addition, specific analyses for chemical contaminants were conducted at periodic intervals by an independent testing facility. Copies of these analyses are maintained at Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, Michigan. Results of the feed and water analysis were
judged to be acceptable.

Animal Welfare
In response to the Final Rules amending the U.S. Animal Welfare Act promulgated by the U.S. Department of Agriculture effective October 30, 1989, the Animal Care and Use Activities (ACUA) required for the conduct of this study were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC). The IACUC has determined that the proposed Activities are in full accordance with these Final Rules. The IACUC assigned File No. Genetic Tox 02 and Animal ID 01 to these Animal Care and Use Activities.

Lymphocyte Cultures
Blood samples were collected by cardiac puncture, following euthanasia with carbon dioxide, from four rats. In this assay, blood samples from individual rats were pooled
and whole blood cultures were set up in RPMI 1640 medium (with 25 mM HEPES, GIBCO, Grand Island, New York) supplemented with 10% heat-inactivated dialyzed fetal bovine serum (GIBCO), antibiotics and antimycotics (Fungizone 0.25 µg/ml; penicillin G, 100 µ/ml; and streptomycin sulfate, 0.1 mg/ml; GIBCO), 30 µg/ml PHA
(HA16, Murex Diagnostics Ltd., Dartford, England), and an additional 2 mM L-glutamine (GIBCO). Cultures were initiated by inoculating approximately 0.5 ml of whole blood/5 ml of culture medium. Cultures were set up in duplicate at each dose level in T-25 plastic tissue culture flasks and incubated at 37°C.

Controls
The solvent selected for dissolving the test material was used as the negative control treatment. Mitomycin C (MMC, Sigma, St. Louis, Missouri, CAS No. 50-07-7) was used
as the positive control chemical for the non-activation assay at a concentration of 0.5 µg/ml (4 h treatment) or 0.05 and 0.075 µg/ml (24 h

treatment), while cyclophosphamide monohydrate (CP, Sigma, CAS No. 6055-19-2) was the positive control for the activation assay at final concentrations of 4 and 6 µg/ml.

In Vitro Metabolic Activation System
S-9 liver homogenate prepared from Aroclor 1254 treated (500 mg/kg) male Sprague-Dawley rats was purchased from Molecular Toxicology, Inc., Boone, North Carolina, and
stored at -100°C or below. Thawed S-9 was reconstituted at a final concentration of 10% (v/v) in a "mix" (O'Neill et al., 1982). The mix consisted of 10 mM $MgCl_2 \cdot 6H_2O$ (Sigma), 5 mM glucose-6-phosphate (Sigma), 4mM nicotinamide adenine dinucleotide phosphate (Sigma), 10mM $CaCl_2$ (Fisher, Fair Lawn, New Jersey), 30 mM KCl (Sigma), and 50 mM sodium phosphate (pH 8.0, Sigma and Fisher). The reconstituted mix was added to the culture medium to obtain the desired final concentration of S-9 in the culture, i.e., 2% v/v. Hence, the final concentration of the co-factors in the culture
medium was 1/5 of the concentrations stated above.

Preparation of the Treatment Solution
The test material was first dissolved in dimethyl sulfoxide (DMSO, Sigma) and further diluted (1:100) with the treatment medium to obtain the desired concentrations. All
prepared stock solutions were submitted to the Analytical Chemistry Laboratory of the testing facility for the verification of test material concentrations. MMC and CP were dissolved directly in treatment medium. The treatment medium was RPMI 1640 with HEPES and antibiotics, without the serum and the PHA. The pH of treatment medium containing approximately 120 µg/ml the test material (above the limit of solubility in culture medium) and medium containing 1% DMSO was determined using a Denver
Basic pH meter (Denver Instrument Co., Arvada, Colorado) and an Osmette A freezing point osmometer (Precision Systems, Inc., Natick, Massachusetts), respectively. There
was no appreciable change in either the pH or osmolality at this concentration as compared to the culture medium with solvent alone (culture medium with the test material, pH = 7.41, osmolality = 421 mOsm/kg H20; culture medium with 1% DMSO, pH = 7.35, osmolality = 429 mOsm/kg H20).

Analytical Verification of Dosing Solutions
The selected concentrations of the test material in the stock solutions used for treatment were verified by the Analytical Chemistry Laboratory, Toxicology & Environmental
Research and Consulting, The Dow Chemical Company, Midland, Michigan. Samples were diluted in an appropriate solvent and analyzed by high performance liquid chromatography (HPLC) with ultra violet (UV) detection.

Identification of the Test System
All test cultures were identified using self adhesive labels containing a code system that identified the test material, experiment number, treatment, and replicate.

Treatment Procedure without Metabolic Activation
Approximately forty-eight hours after initiation of the cultures, the cell suspension was dispensed into 15 ml sterile centrifuge tubes (approximately 5.5 ml/tube, two cultures per dose level). The cells were sedimented by centrifugation and the culture medium removed and saved. The cells were exposed to medium (RPMI 1640, HEPES, and antibiotics) containing the test or positive or negative control treatments for approximately 4 hr at 37°C and the exposure was terminated by washing

the cells with
culture medium. The cells were then placed in individual sterile disposable tissue culture flasks (T-25) along with approximately 4.5 ml of the original culture medium until the time of harvest. The cultures were harvested at approximately 24 hr after treatment initiation (i.e., approximately 20 hr after treatment termination).

A second set of cultures was treated with the test material continuously for 24 hr (approximately 1.5 normal cell cycle length). Stock solutions of the treatments were added directly to the culture flasks at 48 hr after initiation of the cultures and these cultures were harvested 24 hr later.

Treatment Procedure using Metabolic Activation
Approximately 48 hr after initiation of the cultures, the cell suspension was dispensed into sterile disposable centrifuge tubes. The cells were sedimented by centrifugation and the culture medium removed and saved. The cells were exposed to medium (RPMI 1640, HEPES, antibiotics, and S-9) containing the test and positive and negative control treatments for 4 hr at 37°C and the exposure was terminated by washing the cells with culture medium (without serum and PHA).

The cells were then placed in individual sterile disposable tissue culture flasks (T-25) along with 4.5 ml of the original culture media until the time of harvest. The cultures were harvested approximately 24 hr after treatment initiation (i.e., 20 hr after treatment termination).

Harvesting of Cultures and Slide Evaluation
Colcemid was added approximately 3 hr prior to harvest at a final concentration of 0.2 µg/ml. The cells were swollen by hypotonic treatment (0.075 M KCl), fixed with methanol:acetic acid (3:1), dropped on microscope slides, and stained in Giemsa. All slides were coded prior to evaluation. Mitotic indices were determined as the number of cells in metaphase among 1000 cells/replicate and expressed as percentages. One hundred metaphases/replicate were examined, where possible, from coded slides at each
selected concentration of the test chemical and the negative controls (a total of 200 cells/treatment) for structural abnormalities (Buckton and Evans, 1973; Sinha et al., 1984; Gollapudi et al., 1986). In the positive control cultures, 50-75 metaphases/replicate (a total of 100-150 cells/treatment) were examined for abnormalities unless otherwise indicated. The microscopic coordinates of those metaphases containing aberrations were recorded. Only those metaphases that contained 42 + 2 centromeres were scored with the exception of cells with multiple aberrations, in which case accurate counts of the chromosomes were not always possible. Structural chromosomal abnormalities that were counted included chromatid and chromosome gaps, chromatid breaks and exchanges, chromosome breaks and exchanges, and miscellaneous (chromosomal disintegration, chromosomal pulverization, etc.). Those cells having five
or more aberrations/cell were classified as cells with multiple aberrations. Gaps were not included in calculations of total cytogenetic aberrations. In addition, one hundred metaphases/replicate were examined for the incidence of polyploidy. The data was used to calculate the following parameters:

% Cells with aberrations : Aberrant cells (excluding cells with gaps only)/# metaphases evaluated x 100

Aberrations/100 cells : Total aberration (excluding gaps, miscellaneous and severely damaged)/# metaphases evaluated

Statistics

The proportion of cells with aberrations (excluding gaps) was compared by the following statistical methods. At each dose level, data from the replicates were pooled. A two-way
contingency table was constructed to analyze the frequencies of aberrant cells. An overall Chi-square statistic, based on the table, was partitioned into components of interest. Specifically, statistics were generated to test the two global hypotheses of (1) no
differences in average number of cells with aberrations among the dose groups, and (2) no linear trend of increasing number of cells with aberrations with increasing dose (Armitage, 1971). An ordinal metric (0, 1, 2, etc.) was used for the doses in the statistical evaluation. If either statistic was found to be significant at a = 0.05 versus a one-sided increasing alternative, pairwise tests (i.e., control vs. treatment) were performed at each
dose level and evaluated at a = 0.05 again versus a one-sided alternative.

Polyploid cells were analyzed by the Fisher Exact probability test (Siegel, 1956). The number of polyploid cells was pooled across replicates for the analysis and evaluated at a = 0.05. The data was analyzed separately based on the presence or absence of S-9 and based on the exposure time.

For a test to be acceptable, the chromosomal aberration frequency in the positive control cultures should be significantly higher than the negative controls. The aberration frequency in the negative control should be within reasonable limits of the laboratory historical values. A test chemical is considered positive in this assay if it induces a significant dose-related and reproducible increase in the frequency of cells with
aberrations.

1 Fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International)

Result : The analytically detected concentrations of the test material in the stock solutions varied from 91.5 to 97.5% of the target.

4 Hr Treatment Assay
In the 4 hour treatment, cultures were treated with the test material in the absence and presence of S-9 activation at concentrations of 1.9, 3.8, 7.5, 15, 30, 60, and 120 µg/ml. The highest concentration evaluated was based upon solubility limitations. Without metabolic activation, the 60 and 120 µg/ml levels induced excessive toxicity as assessed by reductions in mitotic indices of 70 and 72%, respectively. Cultures treated with 15 and 30 µg/ml had reductions in mitotic indices of 40 and 55%, respectively. The remaining cultures showed little toxicity. Based upon these results, cultures treated with 3.8, 15, and 30 mg/ml were chosen for the determination of chromosomal aberration frequencies and incidence of polyploidy in the absence of S-9 activation.

In the presence of S-9 activation, the highest concentration evaluated (120 mg/ml) induced a 54% reduction in mitotic index. Cells treated with concentrations of 30 and 60 µg/ml had reductions in mitotic indices of 34 and 61%, respectively, while the remaining cultures showed little toxicity. Based upon these results, cultures
treated with 7.5, 30, and 60 µg/ml were selected for evaluating aberrations in the presence of S-9 activation.
Among the cultures treated with the positive control chemicals, 0.5 mg/ml of MMC and 4 mg/ml of CP were selected for evaluation of aberrations in the absence and presence of S-9, respectively.

There were no significant increases in the incidence of polyploid cells in the test material treated cultures as compared to the negative control values.

In the non-activation assay, the frequency of cells with aberrations in the

negative control was 2.0% and the corresponding values at treatment levels 3.8, 15, and
30 µg/ml were 2.5, 6.0, and 2.5%, respectively. In the activation assay, cultures treated with the test material at concentrations of 7.5, 30, and 60 µg/ml had aberrant cell frequencies of 3.5, 3.5, and 2.0%, respectively as compared to the negative control value of 4.0%. Statistical analyses of these data did not identify significant
differences between the negative control and any of the treated cultures either with or without S-9 activation. The frequencies of aberrant cells in the test material treated
cultures were within the laboratory historical background range.

Significant increases in the frequency of cells with aberrations were observed in cultures treated with the positive control chemicals. Aberrant cell frequencies in MMC (without S-9) and CP (with S-9) treated cultures were 14.3% and 29%, respectively.

A second assay with treatment of cultures in the presence of S-9 was not considered necessary in this assay since the results of the initial test yielded clearly negative results.

24 Hr Treatment Assay (without S-9)
Rat lymphocyte cultures were treated continuously for 24 hr with 0.9, 1.9, 3.8, 7.5, 15, 30, 60, and 120 µg/ml of the test material in the absence of S-9 activation. Cultures were harvested 24 hr after treatment initiation.

The higher concentrations tested, (i.e., 60 and 120 µg/ml) showed excessive toxicity as evidenced by mitotic index reductions of 74 and 88%, respectively. Cultures treated with 15 and 30 µg/ml had reductions of 43 and 69%, respectively. The remaining cultures had reductions in mitotic index of 7 to 10% (Table 2C). Based upon these results, cultures treated with 3.8, 15, and 30 µg/ml were selected for determining the chromosomal aberration frequencies.

Among the cultures treated with the positive control chemical, 0.05 µg/ml of was selected for the evaluation of aberrations.

There were no significant increases in the incidence of polyploid cells in test material treated cultures as compared to the negative control values.

In the 24 hr treatment assay, the frequency of cells with aberrations in the negative control was 1.5% and the corresponding values at treatment levels 3.8, 15, and
30 µg/ml were 0, 2.5, and 3.0%, respectively. Statistical analyses of these data did not identify significant differences between the negative control and any of the treated cultures either with or without S-9 activation. The frequencies of aberrant cells in the test material treated cultures were within the laboratory historical background range.

A significant increase in the frequency of cells with aberrations was observed in cultures treated with the positive control chemical (MMC). The aberrant cell frequency was 14%.

Source : The Dow Chemical Company, Midland, MI.

Conclusion : The test material, pentachloropyridine, did not induce a significant increase in the frequency of cells with chromosomal abnormalities at any of the concentrations
evaluated. Hence, it was concluded that under the experimental conditions used, pentachloropyridine was not genotoxic in this in vitro chromosomal aberration test.

Reliability : (1) valid without restriction

22.09.2004 (7)

Type	:	Cytogenetic assay
System of testing	:	Mouse bone marrow cells
Test concentration	:	11.75, 100 mg/kg
Cycotoxic concentr.	:	Not indicated
Metabolic activation	:	no data
Result	:	negative
Method	:	other
Year	:	1993
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Ten male CFLP mice weighing approximately 30 g were used in each experimental group. The animals were given single oral doses of 11.75 mg/kg (1/20 of the i.p. LD50 in mouse) and 100 mg/kg PCP in pharmaceutically pure sunflower oil (Oleum helianthi); parallel to these experiments the solvent (0.1 ml Oleum helianthi per mouse), the positive control (100 mg/kg cyclophosphamide), and the untreated control group were studied. The bone marrow preparation was carried out 24 and 48 hours after treatment (cyclophosphamide: 24 hours after treatment). Following band technique staining, 20 mitoses in metaphase per mouse were evaluated using the technique of Datta et al. (1970). Significance calculations were made by the Fisher probe.
Result	:	No significant increase in the number of cells showing alterations as well as in the frequency of numerical and structural chromosome aberrations could be observed, neither 24 nor 48 hours after treatment with PCP. When the chromosomes of cyclophosphamide-treated animals were examined 24 hours after treatment, total aberrations in bone marrow cells were 78.5% ($p<0.001$). Thus, PCP cannot be regarded as a mutagen in the chosen test system.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(2) valid with restrictions Study does not satisfy the requirements of SIDS-level endpoints.

22.09.2004 (19) (20)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	Days 6-20 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	Until gestation day 21
Doses	:	50, 100, 200, or 400 mg/kg BW/day
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 50 mg/kg bw
NOAEL teratogen.	:	= 200
Method	:	EPA OPPTS 870.3700
Year	:	2003

GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : TEST MATERIAL INFORMATION

Test Material Name
Pentachloropyridine

Chemical Name
2,3,4,5,6-Pentachloropyridine

Synonyms
PCP, Perchloropyridine

Supplier, City, State (lot, reference number)
Dow AgroSciences LLC, Indianapolis, Indiana (T-171C, TSN103958)

Purity/Characterization (method of analysis and reference)
The purity of PCP, lot T-171C, was determined to be > 99% by gas chromatography and liquid chromatography. Compound structure was confirmed by infrared mass spectrometry (IR/MS) and proton and carbon nuclear magnetic resonance (CNMR) analysis.

Characteristics

Appearance (physical state, color)
Gray crystals

Molecular Formula
C_5Cl_5N

Molecular Weight
251.33

TEST SPECIES AND HUSBANDRY

Species and Sex
Rats, time-mated female

Strain and Justification
CD (Crl:CD(SD)IGS BR) rats were selected because of their general acceptance and suitability for toxicity testing, availability of historical background data and the reliability of the commercial supplier.

Supplier and Location
Charles River Laboratories Inc. (Portage, Michigan)

Age and Weight at Study Start
Sexually mature adult, 10-11 weeks of age and weighing approximately 200-250 grams.

Physical and Acclimation
Each animal was evaluated by a laboratory veterinarian or a trained animal/toxicology technician, under the direct supervision of a lab veterinarian to determine their general health status and acceptability for study purposes upon arrival at the laboratory1. The animals were housed one per cage and allowed to acclimate to the laboratory conditions for five days prior to the start of dosing.

Housing
After assignment to study, animals were housed one per cage in stainless steel cages. The relative humidity and temperature were maintained within

a range of 40-70% and
22 ± 1°C with a maximal allowable excursion range of ± 3°C. These values were within the laboratory recommended range for rats. A 12-hour light/dark photocycle was maintained with lights on at 6:00 a.m. and off at 6:00 p.m. Room air was exchanged approximately 12-15 times/hour. Cages had wire-mesh floors and were suspended above catch pans. Cages contained a glass feed crock and a pressure activated nipple-type watering system.

Randomization and Identification
Animals were stratified by gestation day 0 body weight and then randomly assigned to treatment groups using a computer program designed to increase the probability of uniform group mean weights and standard deviations at the start of the study. Rats placed on study were uniquely identified via subcutaneously implanted transponders (BioMedic Data Systems, Seaford, Delaware) which were correlated to unique alphanumeric identification numbers.

Feed and Water
Animals were provided LabDiets Certified Rodent Diet #5002 (PMI Nutrition International, St. Louis, Missouri) in meal form. Feed and municipal water were provided ad libitum. Analyses of the feed were performed by PMI Nutrition International to confirm the diet provided adequate nutrition and to quantify the levels of selected
contaminants. Drinking water obtained from the municipal water source was periodically analyzed for chemical parameters and biological contaminants by the municipal water department. In addition, specific analyses for
chemical contaminants were conducted at periodic intervals by an independent testing facility. Copies of these analyses are maintained at Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland,
Michigan. The results of the feed and water analyses indicated that there were no contaminants present at levels that would interfere with the conduct of the study or
interpretation of the results.

Animal Welfare
In response to the Final Rules amending the U.S. Animal Welfare Act promulgated by the U.S. Department of Agriculture effective October 30, 1989, the Animal Care and Use Activities (ACUA) required for the conduct of this study were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC). The IACUC determined
that the proposed Activities were in full accordance with these Final Rules.

Breeding Procedures
Sexually mature virgin females were naturally mated with males of the same strain (one male:one female) at the supplier's facility. Females were checked for in situ copulation plugs the following morning and those found with such a plug were removed from the males' cages. The day on which a vaginal plug was detected was considered day 0 of
gestation. Gestation day 0 body weights were provided by the supplier, and maintained in the study record. Rats arrived in our laboratory on gestation day 1.

STUDY DESIGN

Experimental Design and Critical Dates
Groups of eight time-mated female CD rats were administered pentachloropyridine by gavage at dose levels of 0, 50, 100, 200, or 400 mg/kg/day on days 6-20 of gestation. This dosing schedule was based on the Health Effects Test Guideline of the United States Environmental

Protection Agency (OPPTS 870.3700 Prenatal Developmental Toxicity Study). Test material administration began on April 8, 2003 and the animals were euthanized on April 23, 2003.

Text Table 1. Study Parameters

Study Parameters	Day(s) of Gestation
Clinical Observations	Daily
Body Weights	0, 6-20, 21 (terminal)
Dosing	6-20
Feed Consumption	3-6, 6-9, 9-12, 12-15, 15-18, 18-21
Maternal Necropsy	21
Organ Weights	21

Reproductive Parameters:

Number of Corpora Lutea	21
Number of Implantation Sites	21
Number of Viable Fetuses	21
Number of Resorptions	21

Route, Method of Administration, Frequency, Duration and Justification
Pentachloropyridine was administered by oral gavage once daily for seven days per week on days 6-20 of gestation. Gavage administration is the preferred route of exposure
specified in the relevant test guideline and will be the route used in the subsequent developmental toxicity study.

Dose Levels and Justification
These dose levels were selected to provide adequate data to establish a maximum tolerated dose and to provide dose-response data for any toxicity observed. The top dose
level of 400 mg/kg/day was based on prior toxicity data (discussed previously) indicating very little toxicity at doses of approximately 250 mg/kg/day, yet lethality at
500 mg/kg/day. In light of this steep dose response, it was considered necessary to set the high dose between 250 and 500 mg/kg/day in order to accurately estimate the
maximum tolerated dose.

Dose Preparation and Analysis
Pentachloropyridine was administered as a suspension in corn oil such that a dose volume of 4 ml/kg body weight yielded the targeted dose. Corn oil was selected as the vehicle based on preliminary method development work. Dose volumes were adjusted daily based on individual body weights.

Analysis

Homogeneity
The low- and high-dose suspensions were analyzed concurrent with the study to verify homogeneous distribution of the test material in vehicle.

Stability
Stability of the 50 and 200 mg/kg/day dose group suspensions were determined concurrent with the study using HPLC with ultraviolet detection and external standards.

Concentration Verification
Concentrations of all dose suspensions were verified in conjunction with the stability and homogeneity analyses.

Retainer Samples
Reference samples were not retained, as this study was less than four

weeks in duration.

In-Life Observations
Clinical examinations were conducted daily throughout the study period. This examination included careful, hand-held evaluations of the skin, fur, mucous membranes, respiration, nervous system function (including tremors and convulsions), swelling, masses and animal behavior at the time of dosing. At the expected time of peak effects,
animals were observed for general behavior and appearance, respiration, nervous system function (including tremors and convulsions) and any other signs of clinical toxicity. In
addition, a cage-side examination was conducted and to the extent possible, the following were evaluated: skin, fur, mucous membranes, respiration, nervous system function
(including tremors and convulsions), animal behavior, moribundity, mortality, and the availability of feed and water. Any animals found dead were necropsied on that day.

Body Weights
Body weights were recorded on day 0 by the supplier, daily during the dosing period, and on day 21 of gestation. Statistical analyses of body weights and body weight gains were performed using data collected on gestations days 0, 6, 9, 12, 15, 18, and 21.

Feed Consumption
Feed consumption was recorded for all animals beginning on day 3 of gestation by weighing feed containers at the start and end of a measurement cycle and consumption was calculated using the following equation:

Feed consumption (g/day) = (initial weight of feed container - final weight of feed container)/
(# of days in measurement cycle)

Anatomic Pathology

Necropsy
On day 21 of gestation, all animals that survived were submitted for a complete necropsy by a team of trained individuals under the direct supervision of a veterinary
pathologist. The animals were weighed, anesthetized with CO2, the tracheas exposed and clamped and the animals decapitated. The eyes were examined in situ by visual
inspection using a moistened glass slide technique. Weights of the liver and kidneys were recorded, and the organ-to-body weight ratios calculated. Sections of liver,
kidneys and any gross lesions were preserved in neutral, phosphate-buffered10% formalin. Histopathologic evaluation of preserved tissues was not performed.

A detailed examination of the uterus for the number of implantations and resorptions, and the ovaries for the number of corpora lutea was performed. The position and
number of early and/or late resorptions and normally developing fetuses were recorded. As the objective of this study was limited to the evaluation of maternal and
developmental toxicity potential, a detailed external examination of individual fetuses was not performed. The fetuses were euthanized via sublingual deposition of sodium
pentobarbital, and discarded. Corpora lutea were not counted for non-pregnant females. The uteri of animals
lacking visible implantations were stained with a 10% aqueous solution of

sodium sulfide (Kopf et al., 1964) and examined for evidence of early resorptions in order to
verify pregnancy status. Any animal that died was submitted for a complete necropsy examination by a veterinary pathologist. This necropsy was performed as described above with the following exceptions. Terminal body weight was not recorded. Representative sections of the liver, kidneys, and gross lesions were preserved in neutral, phosphate-buffered 10% formalin, however, liver and kidney weights were not recorded. During the ovarian and uterine exam, the number of corpora lutea was not recorded.
The degree to which implantation site(s) had developed was determined to the extent possible by external examination (as appropriate for gestational age). Following
external examination, these implantation sites were discarded. Near term fetuses were euthanized as described above.

STATISTICS
Maternal body weights, maternal body weight gains, organ weights (absolute and relative) and feed consumption were evaluated by Bartlett's test for equality of variances.
Based on the outcome of Bartlett's test, a parametric (Steel and Torrie, 1960) or nonparametric (Hollander and Wolfe, 1973) analysis of variance (ANOVA) was performed. If the ANOVA was significant at a = 0.05, analysis by Dunnett's test (a = 0.05; Winer, 1971) or the Wilcoxon Rank-Sum test (a = 0.05; Hollander and Wolfe, 1973) with Bonferroni's correction (Miller, 1966) was performed, respectively. Frequency of pre- and post-implantation loss was analyzed using a Censored Wilcoxon test with Bonferroni's correction (Haseman and Hoel, 1974). The number of corpora lutea, implantations, resorptions per litter and litter size were evaluated using a
nonparametric ANOVA (a = 0.05) followed by the Wilcoxon Rank-Sum test (a = 0.05) with Bonferroni's correction. Pregnancy rates were analyzed using the Fisher exact
probability test (a = 0.05; Siegel, 1956) with Bonferroni's correction. Non-pregnant females, females with resorptions only, or females found to be pregnant after staining of
their uteri were excluded from the appropriate analyses. Statistical outliers were identified, using a sequential method (a = 0.02; Grubbs, 1969), and excluded if justified
by sound scientific reasons. Both Dunnett's test and Bonferroni's correction correct for multiple comparisons to the control group to keep the experiment-wise a at 0.05. Both were reported at the experiment-wise a level.
Because numerous measurements were statistically compared in the same group of animals, the overall false positive rate (Type I errors) was greater than the nominal
a levels. Therefore, the final interpretation of the data considered statistical analyses along with other factors, such as dose-response relationships and whether the results were consistent with other biological and pathological findings and historical control values.

Calculation of Pre- and Post-implantation Loss
· Pre-implantation loss* = (No. corpora lutea-implantations)/No. corpora lutea x 100
· Post-implantation loss* = (No. implantations-viable fetuses)/No. implantations x 100

* Note: Percent pre- and post-implantation loss was determined for each litter, followed by calculation of the mean of these litter values.

1 Fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

Result : Analytical Results

Analyses of all dosing suspensions from the first mix indicated mean concentrations of PCP ranging from 98.8 to 110% of the targeted concentration. A re-mix of the high dose (100 mg/g) suspension was necessary due to an apparent homogeneity problem (see below). The concentration of this second mix of the high-dose suspension assayed at 120% of the targeted concentration. Stability analyses indicated that the test material atconcentrations as low as 1 mg/g was stable in the vehicle for at least 24 days. Analysis of the low-dose suspension indicated that the PCP was homogeneously distributed in the vehicle. As mentioned above, the initial mix of the high-dose suspension indicated apparent heterogeneity, and therefore was not used for dosing. A new mix of the high-dose suspension was prepared and analysis of multiple aliquots at different levels of the storage vessel revealed that PCP was homogeneously distributed. This second mix was used for dosing.

In-Life Observations
Animals 1327 and 1330 from the 400 mg/kg/day dose group were found dead on test day 9 and 8, respectively. Prior to the death of animal 1327, soiling of the perioral (salivation), perineal and perinasal areas was seen on gd 7, 8 and/or 9, with extensive whole body soiling noted on gd 9. Aside from perioral soiling (salivation) on gd 6, animal 1330 did not exhibit any clear treatment-related signs of toxicity prior to death. At necropsy, both of these animals were found to have watery contents in the gastrointestinal tract, liver congestion, and a white, pasty material (presumably test material) in the small intestine. Animal 1327 also had soiling on the skin consistent with its clinical signs, whereas Animal 1330 also exhibited congestion of the adrenals and a cyst in the nonglandular mucosa of the stomach. Animal 1327 was not pregnant (confirmed by sodium sulfide staining), while the uterus of Animal 1330 contained 12 implantations. Due to the excessive degree of toxicity at 400 mg/kg/day, as indicated by these treatment-related deaths, all remaining animals in this group were euthanized on gestation day 9 with no further collection of data.

In the remaining dose groups, increased incidences of perioral soiling (salivation) were apparent at all dose levels. This salivation occurred at the time of dosing and was transient, suggesting that it was a local response to the test material and not a sign of toxicity. Red perinasal soiling was seen at 100 and 200 mg/kg/day and was considered to be treatment-related. Increases in the incidence of perineal soiling and red/dark urine were seen at 200 mg/kg/day only and were also considered to be treatment-related. All other clinical findings were minor in nature and/or occurred on isolated days, and did not appear to be of toxicological significance.

Body Weights
There were no statistically identified differences in the body weights of any treated groups when compared to their respective controls. However, in dams given 200 mg/kg/day, body weight gains during the first few days of dosing (gd 6-9) were significantly decreased. This difference was attributed to PCP exposure.

Feed Consumption
PCP at a dose level of 200 mg/kg/day produced a statistically significant decrease in feed consumption during gd 6-9 relative to their respective controls. This correlated with decreased body weight gain for the same time period. There were, however, no significant differences in the amount of feed consumed for any other time period in the 200 mg/kg/day group, nor at any time in the other treated groups.

Anatomic Pathology

Organ Weights
Dose levels of 100 and 200 mg/kg/day produced statistically significant increases in relative kidney weights of 16% and 20%, respectively. Increases in absolute kidney weight of 16% and 14%, respectively, also were recorded. While not statistically identified, these increases were considered treatment-related. PCP at a dose level of 200 mg/kg/day also produced a statistically significant increase in relative liver weight (26% increase) and although not statistically identified, a 20% increase in absolute liver weight. The 100 mg/kg/day dose level produced a 19% increase in absolute and relative liver weights. Although these increases were not statistically significant, they were considered to be treatment-related. There were no significant effects on absolute or relative weights of the liver or kidney at 50 mg/kg/day.

Gross Pathology
There were no treatment-related gross pathologic observations in animals surviving to the scheduled necropsy. All gross pathologic observations were considered to be spontaneous alterations, unassociated with exposure to PCP.

Reproductive Parameters
Pregnancy rate was low across all groups, including controls, and was likely due to a supplier problem with the
detection of mating. There were no significant treatment related-effects on pregnancy rates, number of corpora lutea, implantations, mean percent preimplantation loss,
number of resorptions per litter, resorptions per litters with resorptions, mean percent postimplantation loss, viable fetuses per litter, or litter size in animals given PCP.

Source : The Dow Chemical Company, Midland, MI.

Conclusion : Oral administration of 400 mg PCP/kg/day to time-mated CD rats resulted in excessive toxicity as evidenced by the spontaneous deaths of two of eight animals. Therefore, the
remaining animals in the 400 mg/kg/day dose group were terminated on day 9 of gestation with no further collection of data. Perioral soiling was seen at all dose levels.
In the remaining animals, treatment-related clinical signs of toxicity were limited to increased incidences of perineal soiling and red/dark urine observed only at
200 mg/kg/day. Maternal body weight was not significantly altered at any dose level, although decreases in body weight gains and food consumption from gestation day 6-9
were statistically identified in the 200 mg/kg/day dose level group. Absolute and relative weights of the liver and kidneys were increased at 100 and 200 mg/kg/day. There were
no treatment-related gross pathological observations, nor were there any effects on reproductive parameters.

Thus, the no-observed-adverse-effect level (NOAEL) for maternal toxicity was 50 mg/kg/day while 200 mg/kg/day was considered a no-observed-effect level (NOEL) for embryo/fetal lethality.

Reliability : (1) valid without restriction

21.09.2004 (7)

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : Gestation Days 6-20
Frequency of treatm. : Daily
Duration of test : Until Gestation Day 21
Doses : 10, 50, 200 mg/kg BW/day

Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 10 mg/kg bw
NOAEL teratogen.	:	= 200 mg/kg bw
NOAEL Fetotoxicity	:	= 50 - mg/kg bw
Result	:	Fetotoxic at maternally toxic dose levels
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	2004
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Species and Sex
Rats, time-mated females

Strain and Justification
CD rats (Crl:CD(SD)IGS BR) were selected because of their general acceptance and suitability for toxicity testing, the availability of historical background data, and the
reliability of the commercial supplier.

Supplier and Location
Charles River Laboratories Inc. (Portage, Michigan)

Age and Weight at Study Start
Sexually mature adult, 10-11 weeks of age and weighing approximately 200-250 g

Physical and Acclimation
Each animal was evaluated by a laboratory veterinarian or a trained animal/toxicology technician, under the direct supervision of a lab veterinarian to determine their general health status and acceptability for study purposes upon arrival at the laboratory1. The animals were placed in their cages (one per cage) and allowed to acclimate to the
laboratory conditions for approximately four days prior to the start of dosing. The animal rooms of the facility are designed to maintain adequate environmental conditions
(temperature, humidity, and photocycle).

Housing
Animals were housed, one per cage, in stainless-steel cages in rooms designed to maintain adequate conditions (temperature, humidity, and photocycle). Room temperature was recorded daily. The relative humidity was maintained within a range of 40-70%. The room temperature was maintained at 22 ± 1°C (with a maximum permissible excursion range of ± 3°C). These values were within the laboratory recommended range for rats. A 12-hour light/dark photocycle was maintained in all animal rooms with lights on at 6:00 a.m. and off at 6:00 p.m. Room air was exchanged approximately 12-15 times/hour. Cages had wire-mesh floors and were suspended above catch pans. Cages contained feed containers and pressure activated, nipple-type watering
systems.

Randomization and Identification
Animals were stratified based upon GD 0 body weights and then randomly assigned to treatment groups using a computer program designed to increase the probability of
uniform group mean weights and standard deviations at the start of dosing. Animals placed on study were uniquely identified via subcutaneously implanted transponders
(BioMedic Data Systems, Seaford, Delaware) which were correlated to unique alphanumeric identification numbers. If a transponder stopped functioning or was lost, it was replaced with a new transponder that correlated with the unique animal number.

Feed and Water
Animals were provided LabDiet Certified Rodent Diet #5002 (PMI Nutrition International, St. Louis, Missouri) in meal form. Feed and municipal water were provided ad libitum. Analyses of the feed were performed by PMI Nutrition International to confirm the diet provided adequate nutrition and to quantify the levels of selected
contaminants. Drinking water obtained from the municipal water source was periodically analyzed for chemical parameters and biological contaminants by the municipal water department. In addition, specific analyses for
chemical contaminants were conducted at periodic intervals by an independent testing facility. Copies of these analyses are maintained at Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland,
Michigan. The results of the feed and water analysis indicated that there were no contaminants present at levels that would interfere with the conduct of the study or
interpretation of the results.

Animal Welfare
In response to the Final Rules amending the U.S. Animal Welfare Act promulgated by the U.S. Department of Agriculture effective October 30, 1989, the Animal Care and Use Activities (ACUA) required for the conduct of this study were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC). The IACUC determined
that the proposed Activities were in full accordance with these Final Rules. The IACUC-approved Animal Care and Use Activities to be used for this study are DART 02 and
Animal ID 01.

Breeding Procedures
Sexually mature, adult virgin females were naturally mated with males of the same strain at the supplier's facility. Females were checked for in situ copulation plugs the following morning and those found with such a plug were removed from the males' cages. The day on which a vaginal plug was detected was considered GD 0. GD 0 body weights were provided by the supplier, and maintained in the study record. Rats arrived in our laboratory on GD 1 or 2.

STUDY DESIGN

Experimental Design and Critical Dates
Groups of 25 time-mated female CD rats were administered PCP by oral gavage at dose levels of 0, 10, 50, or 200 mg/kg/day on GD 6-20.

The following study parameters were evaluated at the designated gestational ages:

Text Table 1. Study Parameters

Study Parameters	Gestation Day
Clinical Observations	Daily
Body Weights	0, 6-20, 21 (terminal)
Dosing	6-20
Feed Consumption	3-6, 6-9, 9-12, 12-15, 15-18, 18-21
Maternal Necropsy	21
Organ Weights (kidneys, liver, gravid uterus)	21

Reproductive Parameters:

Number of Corpora Lutea 21
Number of Implantation Sites 21
Number of Viable Fetuses 21
Number of Resorptions 21

Fetal Data:

Fetal Sex 21
Fetal Body Weights 21
External Examination 21
Visceral Examination 21
Craniofacial Examination Post-necropsy (after fixation in
Bouin's solution
Skeletal Examination Post-necropsy (after skeletal
staining)

Test material administration began for the first group of rats on 02 November 2003 and the last group of animals was necropsied on 02 December 2003.

Route, Method of Administration, Frequency, Duration and Justification
Test material was administered daily by oral gavage from GD 6-20 as recommended by the applicable guideline.

Dose Levels and Justification

Text Table 2. Dose Levels

Dose Levels (mg/kg/day)	No. of Rats/Dose Level
0	25
10	25
50	25
200	25
TOTAL	100

These dose levels were selected based on the preliminary results of the probe study (see study summarized as ordinate 1). The high-dose of 200 mg/kg was expected to
induce overt signs of maternal toxicity. The lower dose levels were selected to provide dose response data for any toxicity observed in high-dose group rats.

Dose Preparation and Analysis
Dose suspensions were prepared in corn oil at concentrations of 0, 2.5, 12.5, and 50 mg/ml and administered a dose volume of 4 ml/kg body weight in order to achieve the targeted dose levels. Dose volumes were adjusted daily based on individual body weights.

Analysis

Homogeneity
Dosing suspensions were analyzed prior to the start of dosing to verify homogeneous distribution of the test material in the vehicle.

Stability
PCP was found to be stable in corn oil at concentrations ranging from 1 mg/g up to 50 mg/g for at least 24 days.

Concentration Verification
Analysis of all dosing suspensions were initiated prior to the start of dosing using high performance liquid chromatography (HPLC) with ultraviolet detection and
external standards to determine concentrations.

Retainer Samples
Reference samples (one/dose/mix) were retained and stored at ambient temperature in sealed vials in a manner consistent with the sample retention policy of the laboratory.

STUDY SPECIFIC PARAMETERS

In-Life Observations
Clinical examinations were conducted daily throughout the study period. This examination included a careful, hand-held evaluation of the skin, fur, mucous membranes, respiration, nervous system function (including tremors and convulsions), unusual swelling or masses, and animal behavior. In addition, at least once each day a
cage-side examination was conducted and to the extent possible, the following were evaluated: skin, fur, mucous membranes, respiration, nervous system function (including
tremors and convulsions), animal behavior, moribundity, mortality, and the availability of feed and water.

Moribund animals that were not expected to survive until the next observation period, and any animals found dead, were necropsied that day.

Body Weights
Body weights were recorded on GD 0 by the supplier, daily during the dosing period, and at necropsy (GD 21). Statistical analysis of body weights was performed using data collected on GD 0, 6, 9, 12, 15, 18, and 21. Statistical analysis of body weight gains was conducted for the following intervals: GD 0-6, 6-9, 9-12, 12-15, 15-18, 18-21, 6-21, and 0-21.

Feed Consumption
Feed consumption was recorded for all animals on GD 3-6, 6-9, 9-12, 12-15, 15-18, and 18-21 by weighing feed containers at the start and end of a measurement cycle. Feed consumption was calculated using the following equation:

Feed consumption (g/day) = (initial weight of feed container - final weight of feed container)/
(# of days in measurement cycle)

Anatomic Pathology

Necropsy
On GD 21, all surviving females (not fasted) were euthanized by CO_2 inhalation and a limited gross pathologic examination (necropsy) was performed. The sequence of
the maternal necropsies was counterbalanced across groups (e.g., control, high, middle, low) to control for potential confounding influences of timing on fetal growth
and skeletal ossification.

The maternal necropsy included an examination of the external tissues and all orifices. The skin was reflected from the carcass, the thoracic and abdominal cavities
were opened, and the viscera was examined. The stomach, liver, and kidneys were dissected from the carcass and were incised. Any obvious

gross pathologic alterations were recorded, and the weight of the liver, kidneys, and gravid uterus was recorded. The ratios of liver and kidney weights to terminal body weight were calculated. Representative sections of liver, kidneys, and gross lesions were preserved in neutral, phosphate-buffered 10% formalin. Transponders were removed and placed in jars with the tissues. A detailed examination of the reproductive tract was performed and the number and position of implantations, viable fetuses, dead fetuses, and resorptions was recorded. Resorptions were classified as either "early" or "late" based on the presence (late resorption) or absence (early resorption) of grossly recognizable embryonic/fetal form, while a "dead fetus" indicated a very recent death as evidenced by a lack external degenerative changes. For females with one or more viable fetuses, the number of ovarian corpora lutea was counted. The uteri of females lacking visible implantations was stained with a 10% aqueous solutio n of sodium sulfide (Kopf et al., 1964) and examined for evidence of early resorptions in order to verify pregnancy status.

The sex of all fetuses was recorded and the body weight of all viable fetuses determined. All fetuses were given an external examination that included observations on body proportions, the head and face (including closure of the palate), abdomen, spine, extremities, genitalia, rectum, and tail. All viable fetuses were euthanized by sublingual administration of a sodium pentobarbital solution. At least one-half of all the fetuses in each litter was chosen randomly using a computer program and a visceral examination was conducted by dissection under a low power stereomicroscope for evidence of visceral alterations (Staples, 1974; Stuckhardt and Poppe, 1984). The visceral examination included observation of the thymus, trachea, esophagus, lungs, great vessels, heart (external and internal), liver, gastrointestinal tract, pancreas, spleen, kidney (sectioned), adrenal glands, ureters, bladder, and reproductive organs. The heads of these fetuses were removed, placed in Bouin's fixative and serially sectioned to allow for inspection of the eyes, brain, nasal passages, and tongue (Wilson, 1965). Remaining fetuses not selected for visceral examination were then skinned, eviscerated, preserved in ethyl alcohol (95%), and double stained with Alcian Blue and Alizarin Red S for cartilage and bone respectively, according to methods based on Trueman et al. (1999). After staining, skeletons were macerated and cleared. A thorough evaluation of the fetal skeleton was conducted on the remaining fetuses not selected for visceral examination. However, a fetus may have been intentionally changed from one selected for visceral examination to one processed for skeletal examination (and vice versa) if it was deemed that such examination would provide more meaningful data about a suspected abnormality.

All fetal alterations were classified as variations or malformations. A variation was defined as a divergence beyond the normal range of structural constitution that may not have adversely affected survival or health. A malformation was defined as a permanent structural change that may adversely affected survival, development or function and/or which occurred at a relatively low incidence in the specific species/strain. Maternal necropsy and fetal examinations were conducted such that investigators were blind to treatment. During routine working hours, any animals found dead were necropsied on that day. This necropsy was performed as described above with the following exceptions: 1) animals submitted alive for necropsy were euthanized by the inhalation of CO2 and subsequent decapitation, 2) the head was removed, the cranial cavity opened and the brain, pituitary, and adjacent cervical tissues were examined, 3) all viscera were dissected from the carcass and re-examined, 4) terminal body weight, liver, kidney, and gravid uterine weights were not recorded, 5) the number of corpora lutea and the sex and body weight of fetuses from these animals was not recorded), and 6) evaluation of the implantations was limited to a general assessment of viability and external development (to the extent possible).

STATISTICS AND CALCULATIONS
Maternal body weights, maternal body weight gains, organ weights (absolute and relative), fetal body weights, and feed consumption were evaluated by Bartlett's test (alpha = 0.01; Winer, 1971) for equality of variances. Based on the outcome of Bartlett's test, a parametric (Steel and Torrie, 1960) or nonparametric (Hollander and Wolfe, 1973) analysis of variance (ANOVA) was performed. If the ANOVA was significant at alpha = 0.05, analysis by Dunnett's test (alpha = 0.05; Winer, 1971) or the Wilcoxon Rank-Sum test (alpha = 0.05; Hollander and Wolfe, 1973) with Bonferroni's correction (Miller, 1966) was performed, respectively. Feed consumption values were excluded from analysis if the feed was spilled or scratched.

Frequency of pre- and post- implantation loss (calculations shown below), and fetal alterations were analyzed using a censored Wilcoxon test (Haseman and Hoel, 1974) with Bonferroni's correction. The number of corpora lutea, implantations, and litter size was evaluated using a nonparametric ANOVA (alpha = 0.05) followed by the Wilcoxon Rank-Sum test (alpha = 0.05) with Bonferroni's correction. Pregnancy rates were analyzed using the Fisher exact probability test (alpha = 0.05; Siegel, 1956) with Bonferroni's correction. Fetal sex ratios were analyzed using a binomial distribution test. Females lacking visible implantations at the scheduled necropsy were excluded from the appropriate analyses. Statistical outliers were identified using a sequential method (alpha = 0.02; Grubbs, 1969), but were not excluded unless justified by sound scientific reasons unrelated to treatment. Both Dunnett's test and Bonferroni's correction corrected for multiple comparisons to the control groups and kept the experiment-wise alpha at 0.05. Both were reported at the experiment-wise alpha level.

Because numerous measurements were statistically compared in the same group of animals, the overall false positive rate (Type I errors) was greater than the nominal alpha levels. Therefore, the final interpretation of the data considered statistical analyses along with other factors, such as dose-response relationships and whether the results were consistent with other biological and pathological findings and historical control values.

Calculation of Pre- and Post-Implantation Loss
· Pre-implantation loss* = (No. corpora lutea - implantations) / No. corpora lutea X 100
· Post-implantation loss* = (No. implantations - viable fetuses) / No. implantations X 100

* Note: Percent pre- and post- implantation loss were determined for each litter, followed by calculation of the mean of these litter values.

1 Fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

Result : Analytical
Analysis of all dosing suspensions from the first of two mixes revealed mean concentrations of PCP ranging from 94.0% to 101% of targeted

concentrations. PCP was homogeneously distributed throughout the dosing suspensions as verified by analysis of multiple aliquots at different levels in the storage vessels.

In-Life Observations
Examinations performed on all animals prior to the start of dosing (GD 0-6) revealed incidental abrasions, which were apparently inflicted during breeding at the supplier's facility. One middle-dose rat (# 4734) appeared thin upon arrival (GD 1-4), but was otherwise healthy. By GD 5, this animal appeared normal. One animal (# 4736) from the middle-dose group was found dead on GD 8. A gross necropsy examination was performed. This examination revealed general cyanosis, and visceral congestion, but the cause of death was not determined. This animal was pregnant.

Oral administration of PCP produced an increase in transient, post-dosing salivation (recorded as clear, perioral soiling) in 2 out of 25 animals in the mid-dose group and 24 out of 25 animals in the high-dose group on various days during the dosing period. In one high-dose animal, the soiling was extensive and was observed beyond the perioral region. The incidence of this soiling among affected animals was transient and sporadic across test days and in only one case, appeared prior to dosing (on GD 13). No low-dose animals showed signs of pre- or post-dosing salivation. The mechanism of this salivation effect is unknown, but is likely related to a localized reaction to the test material.

Additionally, 7 out of 25 high-dose animals (all of which showed signs of perioral soiling), had urine soiling at least once during dosing. These observations, though treatment related, were not associated with any persistent toxic effect.

Body Weights
The body weight of animals administered 200 mg/kg/day was significantly decreased relative to control on GD 12, 15, 18, and 21. Also, decreases in weight gain were statistically significant in the high-dose group on GD 6-9, 9-12, 18-21, 6-21, and 0-21 compared to control.

Feed Consumption
There were no significant differences in feed consumption between the mid- and low-dose groups and controls in any of the intervals examined. In the high-dose group, differences in feed consumption were statistically significant compared to control only during the GD 6-9 and 9-12 intervals.

Anatomic Pathology

Organ Weights
Administration of PCP at dose levels of 50 and 200 mg/kg/day produced statistically-significant increases, relative to control, in absolute and relative kidney weights (increased by 6.8% and 17.3%, and 8.6% and 27.1%, respectively). PCP also produced treatment-related increases in absolute and relative liver weight (by 8.2% and 17.1%, respectively) in high-dose animals and these increases were statistically significant. In mid-dose rats, absolute and relative liver weights were also increased (by 6.2 and 7.6% compared to controls, respectively), but only the increase in relative liver weight was statistically significant. Overall, increases in kidney and liver weights were considered

treatment related. There were no significant effects on absolute or relative liver or kidney
weights at 10 mg/kg/day.

Gross Pathology
In one high-dose animal (#4759), the size of both kidneys was increased and each had a pale cortex. Because of increases in relative and absolute kidney weights in high-dose animals, these effects were likely related to treatment, despite its low incidence. The kidneys of all other high-dose animals were unremarkable.

All observations were considered to be spontaneous alterations, and unassociated with exposure to PCP.

Reproductive Parameters
There were no treatment-related effects on pregnancy rates, resorption rates, litter size, numbers of corpora lutea or
implantations, percent preimplantation loss, percent postimplantation loss, fetal sex ratios, or gravid uterine weights at any dose level.

At the highest dose level, fetal body weights of male fetuses, female fetuses, and both sexes combined were less than controls and these differences were statistically
significant. This effect on fetal body weight was correlated with decreased body weight in high-dose dams and was likely subsequent to maternal toxicity.

Fetal Alterations
The incidence of irregular pattern of ossification of the sternebrae in the low- and high-dose groups was
significantly different than control. However, because the incidences were less than control, this result was dismissed as due to random variation across all groups. There were no statistically- significant differences in the incidence of any other fetal alteration in any of the treated groups compared to controls. The small number of
alterations observed in fetuses from dams administered PCP either occurred at low frequencies and/or were not dose related.

Text Table 3. Summary of Fetal Malformations

Dose Group	Dam ID#	Fetus ID#	Malformation
Control	4678	3	Irregular cartilage in a thoracic centrum.
			Extra thoracic rib and vertebrae.
			Fused thoracic ribs
		5	Extra thoracic rib, vertebrae and centra
	4696	15	13th thoracic rib missing
	4701	9	Sternoschisis
10 mg/kg/day	N/A1	N/A	N/A
50 mg/kg/day	4742	15	Macrophthalmia
	4748	5	Extra thoracic rib, vertebrae and centra
200 mg/kg/day	4756	13	Anophthalmia
			Domed skull

1N/A No fetal malformations were observed in the 10 mg/kg/day group.

Source : The Dow Chemical Company, Midland, MI.
Conclusion : Oral gavage administration of PCP at a dose level of 200 mg/kg/day caused maternal toxicity as evidenced by decreases in body weight, body weight gain, feed consumption, and increases in kidney and liver weight. Treatment-related clinical observations included clear, perioral soiling in the high and middle-dose group, and urine soiling in the high-dose group. Developmental effects were limited to decreased fetal body weight at 200 mg/kg/day. There were no other effects on fetal development at any dose level.

Therefore, under the conditions of this study, the no-observed-effect level (NOEL) for maternal toxicity was 10 mg/kg/day and the NOEL for developmental toxicity was
50 mg/kg/day.
Reliability : (1) valid without restriction
22.09.2004 (7)

Species : mouse
Sex : female
Strain : DBA
Route of admin. : gavage
Exposure period : Days 6-15 of gestation
Frequency of treatm. : Daily during treatment period
Duration of test : Until gestation day 18
Doses : 100 mg/kg
Control group : no
Method : other
Year : 1993
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Embryotoxic effects were studied following oral administration of 100 mg/kg PCP in sunflower oil (Oleum helianthi) daily to pregnant Halle:DBA and Halle:AB mice on days 6-15 of gestation. On day 18 of gestation the mice were killed and the reproductive status was determined (number of corpora lutea and dead and live fetuses; the latter were examined for gross malformations). The data were analyzed statistically using the Chi quadrate test.
Result : There were no significant changes in the number of fetal deaths, the weight of live embryos and the rate of malformations after PCP treatment.
Source : The Dow Chemical Company, Midland, MI
Reliability : (2) valid with restrictions
No examinations for visceral or skeletal malformations were conducted.
22.09.2004 (20)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

Type : other: TOPKAT and DEREK QSAR Analysis

Attached document : Chlorinated Pyridines.xls
pentachloropyridine.doc

08.12.2005

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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(8) Clifford, Dennis A. (1968). Automatic measurement of total oxygen demand: a new theoretical method. Presented at Purdue University, Lafayette, IN.

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10. Summary and Evaluation

10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT

201-16113

Date: 18 February 2000

I U C L I D

D a t a s e t

Existing Chemical	Substance ID: 2402-79-1
CAS No.	2402-79-1
EINECS Name	2,3,5,6-tetrachloropyridine
EINECS No.	219-283-9
Molecular Formula	C5HCl4N

Dataset created by: EUROPEAN COMMISSION - European Chemicals Bureau

This dossier is a compilation based on data reported by the European Chemicals Industry following 'Council Regulation (EEC) No. 793/93 on the Evaluation and Control of the Risks of Existing Substances'. All (non-confidential) information from the single datasets, submitted in the IUCLID/HEDSET format by individual companies, was integrated to create this document.

The data have not undergone any evaluation by the European Commission.

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Chapters:	all
Edition:	Year 2000 CD-ROM edition
Flags:	non-confidential

1.0.1 OECD and Company Information

Name: The Dow Chemical Company
Midland, MI

1.0.2 Location of Production Site

Name: The Dow Chemical Company
Midland, MI

1.0.3 Identity of Recipients

–

1.1 General Substance Information

Substance type: organic
Physical status: solid

1.1.1 Spectra

1.2 Synonyms

– Pyridine, 2,3,5,6–tetrachloro
Source: Dow Chemical Company

– Sym–tet
Source: Dow Chemical Company

– TCP
Remark: Abbreviation used throughout the document.
Source: Dow Chemical Company

(1)

1.3 Impurities

–

1.4 Additives

–

1.5 Quantity

–

1.6.1 Labeling

–

1.6.2 Classification

1.7 Use Pattern

–

1.7.1 Technology Production/Use

–

1.8 Occupational Exposure Limit Values

Type of limit: other: see remark
Limit value:
Remark: TLV (US), OES (UK), MAC (NL), and MAK (GE) have not been established. The Dow Industrial Hygiene Guide (IHG) or time weighted average exposure limit is 2mg/m3 (0.223 ppm) of TCP.
Source: Dow Chemical Company

1.9 Source of Exposure

Remark: WORKER: The Dow Chemical Company is the sole producer of TCP within the OECD member countries. TCP is used solely as an intermediate in the synthesis of chlorpyrifos and is produced at two sites within the US. The product is shipped to a single chlorpyrifos production site in the US and a single chlorpyrifos production site in the UK. A third, minor use site, is located outside the OECD member countries. The production of TCP and chlorpyrifos is highly controlled through engineering of the production facilities in order to enclose the processes and prevent exposure. In conclusion, the number of workers potentially exposed to TCP and the level (concentration) of exposure is low in that there are only two production sites and two use sites within the OECD member countries, the production and use is limited to a single company (DOW), the synthesis and use is highly controlled to prevent exposure, and worker activity is governed by an extensive hygiene and safety program.

CONSUMER: There is no significant consumer exposure to TCP as this chemical is not sold as a consumer product and is not found in the end product in significant quantities (1%).

ENVIRONMENT: The US plant is constructed with secondary containment around all process equipment and process areas. No spills contact surface water and no process–contact water is discharged to surface waters. No TCP material is sent to landfill from the production process. All wastes containing TCP are incinerated.

Source: Dow Chemical Company (2)

1.10.1 Recommendations/Precautionary Measures

1.10.2 Emergency Measures

–

1.11 Packaging

–

1.12 Possib. of Rendering Subst. Harmless

–

1.13 Statements Concerning Waste

–

1.14.1 Water Pollution

–

1.14.2 Major Accident Hazards

–

1.14.3 Air Pollution

–

1.15 Additional Remarks

Remark: no additional remarks
Source: Dow Chemical Company

1.16 Last Literature Search

1.17 Reviews

1.18 Listings e.g. Chemical Inventories

2.1 Melting Point

Value: = 90.5 degree C
Method: other: Differential scanning calorimeter (DSC)
Year: 1990
GLP: no
Source: Dow Chemical Company

(3)

2.2 Boiling Point

Value: = 251.6 degree C at 1013 hPA
Method: other: not specified
GLP: no
Source: Dow Chemical Company

(4)

2.3 Density

Type:
Value:
Remark: no data available
Source: Dow Chemical Company

2.3.1 Granulometry

–

2.4 Vapour Pressure

Value: = .0267 hPa at 25 degree C
Method: other (calculated)
Year: 1990
GLP: no
Remark: The Antoine equation was used to calculate value.
Source: Dow Chemical Company (3)

Value: = 1.3332 hPa at 74 degree C
Method: other (calculated)
Year: 1990
GLP: no
Remark: The Antoine equation was used to calculate value.
Source: Dow Chemical Company (3)

Value: = 10.932 hPa at 112 degree C
Method: other (measured)
Year: 1990
GLP: no
Remark: Ebulliometer was used to measure value. Values were obtained for a temperature range of 112 to 251 deg. Celsius.
Source: Dow Chemical Company (3)

2.5 Partition Coefficient

log Pow: = 3.32 at 25 degree C
Method: other (measured)
Year: 1967
GLP: no
Source: Dow Chemical Company
Test condition: Partition coefficient was measured using an analytical determination at an assumed temperature of 25 deg. Celsius (Temp. not defined). (5)

log Pow: = 3.627 at 25 degree C
Method: other (calculated)
Year: 1986
GLP: no
Source: Dow Chemical Company
Test condition: Partition coefficient was calculated using the Pomona–MedChem structural fragment method at an assumed temperature of 25 deg. Celsius (Temp. not defined). (6)

2.6.1 Water Solubility

Value: < 10 mg/l at 10 degree C
Qualitative: of very low solubility
Method: other: TOD analysis
Year: 1975
GLP: no
Source: Dow Chemical Company (7)

Value: = 22.6 mg/l at 20 degree C
Qualitative: of low solubility
Method: OECD Guide–line 105 "Water Solubility"
Year: 1981
GLP: yes
Source: Dow Chemical Company
Test condition: Column Elution method was used. The pH of the eluant averaged 6.76 ±0.05. (8)

Value: = 29.8 – 30.2 mg/l at 23 degree C
Qualitative: of low solubility
Method: OECD Guide–line 105 "Water Solubility"
Year: 1981
GLP: yes
Source: Dow Chemical Company
Test condition: Shaker Flask method was used. The pH of the saturated TCP solution was 6.82. (8)

2.6.2 Surface Tension

–

2.7 Flash Point

Value:
Type:
Method:
Year:
Remark: no data available
Source: Dow Chemical Company

2.8 Auto Flammability

Value:
Remark: no data available
Source: Dow Chemical Company

2.9 Flammability

Result:
Remark: no data available
Source: Dow Chemical Company

2.10 Explosive Properties

Result:
Remark: no data available
Source: Dow Chemical Company

2.11 Oxidizing Properties

Result:
Remark: no data available
Source: Dow Chemical Company

2.12 Additional Remarks

Remark: no additional remarks
Source: Dow Chemical Company

3.1.1 Photodegradation

Type: other: air and water
Light spect: = 200 – 900 nm
DIRECT PHOTOLYSIS
Halflife t1/2: ca. 7 day
Degradation: ca. 50 % after 7 day
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm3
Rate constant: = .0000000000000152 cm3/(molecule * sec)
Degradation: ca. 50 % after 1050 day
Method: other (calculated): see test condition
Year: 1981 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Result: – The photodegradation of TCP can occur by direct photolysis in air and water, and by photooxidation via hydroxyl radical attack in the atmosphere.
– For direct photolysis in the air, the expected half–life of TCP would be approximately 1 week.
– For direct photolysis in water, at an average water column depth of 50 cm, the expected half–life of TCP would be approximately 1 year.
For photooxidation in the atmosphere, a computer model estimated the half–life of TCP to be 3 years. The combined photodegradation processes investigated provided evidence that TCP would be expected to degrade photolytically in the environment. The photooxidation of TCP is directly dependent on light intensity (quantum yield ranged from 0.001–0.1)
Source: Dow Chemical Company
Test condition: for method see:
– ECETOC Technical Report No. 3 (1981) "An assessment of test methods for photodegradation of chemicals in the environment", p. 61
– Harris J (1990) "Rate of aqueous photolysis", in: Handbook of chemical property estimation methods, Lyman et al. (eds.), Amer Chem Soc, Washington, DC., pp 8–1 to 8–43 (8)

3.1.2 Stability in Water

Type: abiotic
Method: OECD Guide–line 111 "Hydrolysis as a Function of pH"
Year: 1981 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Result: TCP was hydrolytically stable at pHs of 4, 7, or 9 up to a temperature of 70 deg. Celsius. TCP recovery was >98% after 10 days at pH 9 and 70 deg. Celsius. No degradation products were detected following analyses by high pressure liquid chromatography.
Source: Dow Chemical Company (8)

3.1.3 Stability in Soil

Type: **Radiolabel:**
Concentration:
Cation exch. capac.
Microbial biomass:
Method:
Year: **GLP:**
Test substance:
Remark: no data available
Source: Dow Chemical Company

3.2 Monitoring Data (Environment)

Type of measurement:
Medium:
Remark: no data available
Source: Dow Chemical Company

3.3.1 Transport between Environmental Compartments

Type: volatility
Media: water – air
Method: other: (estimation)
Year:
Result: The Henry's Law Constant is estimated to be 2.339E–4 atm.m3/mol.
Source: Dow Chemical Company (8)

Type: volatility
Media: water – air
Method: other: (estimation)
Year:
Result: The air–water partition coefficient, H, is estimated to be 9.746E–3.
Source: Dow Chemical Company (8)

3.3.2 Distribution

Media: air – biota – sediment(s) – soil – water
Method: Calculation according Mackay, Level I
Year: 1981
Method:

The model accounted for six separate environmental compartments: air, water, soil, sediment, suspended aquatic matter and biota. The volume dimensions of the compartments were defined and constant, for calculations on equilibrium distribution of a fixed amount of non–reactive test chemical between each compartment. Calculations were based on fugacity and utilized various physical/chemical parameters including: molecular weight, water solubility, vapor pressure, octanol/water partition coefficient (Kow) and Henry's Law constant.

Result: The model simulations estimated that, at equilibrium, ca. 86% of the total TCP would ultimately volatilize into the atmosphere. The high degree of volatilization was most likely due to the relatively high vapor pressure of TCP. Less of the material was expected to remain in aqueous solution ca. 10%) since the water solubility of TCP was relatively low (ca. 23mg/l using the column elution method). The model used the physical properties of Kow and the sorption coefficient (Koc) to estimate the affinity of TCP for soil and sediment particles. Based on the log Kow of 3,322 and an estimated log Koc of 3.128, less than 2% each of the total TCP concentration was predicted to sorb onto soil or sediment particles. None of the test chemical was expected to partition into suspended aquatic matter or biota. In conclusion, due to the relatively high volatility and low water solubility of TCP, volatilization into the atmosphere would be the primary transfer mechanism. Rates of transfer for hydrolysis and biodegradation are relatively slow and would not contribute significantly to the removal of TCP from the environment. The dominant mechanism for removal of TCP from the environment would be due primarily to photodegradation.
Source: Dow Chemical Company (1)

3.4 Mode of Degradation in Actual Use

Remark: no data available
Source: Dow Chemical Company

3.5 Biodegradation

Type: aerobic
Inoculum: other: Secondary effluent from municipal waste water treatment plant
Concentration: 1 mg/l related to Test substance
Degradation: = after 28 day
Result: under test conditions no biodegradation observed
Method: OECD Guide–line 301 A (new version) "Ready Biodegradability: DOC Die Away Test"
Year: 1981 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Remark: Experiments were performed to examine the potential for biodegradation of TCP in municipal activated sludge. Although some loss of TCP was observed, there were no significant differences in the rate of disappearance between the killed controls and biologically active samples. Both experiments (killed and active) showed a long half–life of 95 and 126 days, respectively. The pseudo first–order rate constants, K (observed), for the active samples was 5.52 E–3/day. The difference in half–lives could be attributed to analytical variability. The loss of TCP over time was most likely due to volatilization and not biodegradation. According to OECD, the results provide evidence that TCP is not readily biodegradable, nor does it possess inherent biodegradability. These results are consistent with others that suggest chlorinated pyridines, in general, are resistant to biodegradation.
Source: Dow Chemical Company
Test condition: Inoculum was adjusted to 5.0±3.0E7 cells/ml. Study was performed according to the "Modified AFNOR Test". (8)

3.6 BOD5, COD or BOD5/COD Ratio

Method: other: see test condition
Concentration: 1 mg/l related to Test substance

Result: TCP had no inhibitory effects on the viability of the test inoculum (secondary effluent seed). BOD is estimated to be very low

Source: Dow Chemical Company
Test condition: The ThOD is 0.811 part/parts. TCP was added to an inoculum concomitant with glucose/glutamic acid. (8)

3.7 Bioaccumulation

Species:
Exposure period:
Concentration:
BCF:
Elimination:
Method:
Year: **GLP:**
Test substance:
Remark: no data available

Source: Dow Chemical Company

3.8 Additional Remarks

Remark: no additional remarks
Source: Dow Chemical Company

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: flow through
Species: Oncorhynchus mykiss (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** yes
NOEC: = .33
LC0: = .94
LC50: = 1.5
Method: OECD Guide–line 203 "Fish, Acute Toxicity Test"
Year: 1984 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Remark: Additional LC50 values determined by linear interpolation were as follows: 24hr = 2.3 mg/l; 48hr = 1.5 mg/l; 72hr =1.5 mg/l
Source: Dow Chemical Company (9)

Type: static
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no data
LC0: = 1
LC100: = 2
—– :
Method: other: not specified
Year: **GLP:** no data
Test substance: as prescribed by 1.1 – 1.4
Remark: LC50 was not specified. Maximum safe concentration was 1mg/l, partial kill concentration was 1.5 mg/l and concentration with 100% fatalities was 2 mg/l.
Source: Dow Chemical Company (10)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring**: yes
NOEC: = 1.1 (filtered samples); 1.27 (unfiltered samples)
LC50 : = 2.05 (filtered samples); 2.14 (unfiltered samples)
Method: OECD Guide–line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year: 1984 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Remark: The mortality threshold concentration for filtered and unfiltered samples were 2.05 and 2.14 mg/l, respectively. The NOEC and LC50 were 1.10 and 2.05 mg/l for filtered and 1.27 and 2.14 mg/l for u unfiltered samples. TCP is moderate lytoxic to Daphnia magna Straus according to the categorization system used by the U.S. EPA.
Source: Dow Chemical Company
Test condition: 48–hour LC50 values were calculated by the probit method. Values are given for filtered and unfiltered samples (1.93 and 2.13 mg/l, respectively). (11)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Selenastrum capricornutum (Algae)
Endpoint: biomass
Exposure period: 120 hour(s)
Unit: mg/l
NOEC: = 3.3 **Analytical monitoring:** yes
EC10: = 3
EC50: = 14.1
— :
Method: OECD Guide–line 201 "Algae, Growth Inhibition Test"
Year: 1984 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4

Remark: - NOEC and EC50 (120–hour) for biomass calculated on the basis of the algal assay medium (AAM) control with and without acetone. Values calculated on the basis of the AAM control with acetone were 3.3 mg TCP/l and 13.9 mg TCP/l, respectively. – Compared to the AAM control without acetone the 72– and 96–hour NOEC's were 6.8 and 2.3 mg/l and the 72– and 96–hour EC50's were 14.3 and 14.4 mg/l, respectively. – Compared to the AAM control with acetone the 72– and 96–hour NOEC's were 6.8 and 2.3 mg/l and the 72– and 96–hour EC50's were 16.8 and 14.1 mg/l, respectively.
Source: Dow Chemical Company
Test condition: Two control sets were used, an algal assay medium (AAM) control without acetone and an AAM control with acetone. (12)

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 120 hour(s)
Unit: mg/l **Analytical monitoring:** yes
EC10: = 1.9
EC50: = 8.8
— :
Method: OECD Guide–line 201 "Algae, Growth Inhibition Test"
Year: 1984 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Remark: – NOEC's for growth rate were not calculated or calculable. EC10 and EC50 (120–hour) for growth rate calculated on the basis of the AAM control with acetone was 1.6 and 8.2 mg TCP/l (calculations on the basis of AAM control without acetone see below).
– The 72– and 96–hour EC50 values were 11.7 and 9.7 mg/l AAM control without acetone and 9.7 and 8.5 mg/l AAM control with acetone, respectively.
Source: Dow Chemical Company
Test condition: Two control sets were used, an algal assay medium (AAM) control without acetone and an AAM control with acetone. (12)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: other: Agar plates
Species: other bacteria: Salmonella typhimurium (strain TA100)
Exposure period:
Unit: **Analytical monitoring:**
Toxicity: > 50
Method: other: OECD Guide–line 471
Year: 1983 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Remark: Toxicity was observed at dose levels 50, 166.7, 500, 1667, and 5000 µg TCP/plate without metabolic activation. With metabolic activation toxicity was noted at 166.7 µg TCP/plate and higher concentrations.

Source: Dow Chemical Company
Test condition: Toxicity tests were done with and without metabolic activation system. Tested concentration ranged from 5 to 5000µg TCP/plate. Overtly toxic concentrations were visualized as showing no bacterial growth on the plate (i.e. absence of background lawn). Lower levels of toxicity may be seen as a thin or sparse bacterial lawn, a reduction in the number of revertants, or the appearance of microcolonies (overgrown background lawn). (13)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Species:
Endpoint:
Exposure period:
Unit: **Analytical monitoring:**
Method: **GLP:**
Year:
Test substance:
Remark: no data available
Source: Dow Chemical Company

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Endpoint: mortality
Exposure period: 21 day
Unit: mg/l **Analytical monitoring:** yes
NOEC: = .31
LOEC: = .61
LC50 : = 1.94
Method: OECD Guide–line 202, part 2 "Daphnia sp., Reproduction Test"
Year: 1984 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Result: For mortality MATC was determined to be 0.43 mg/l.
Source: Dow Chemical Company
Test condition: A flow–through life–cycle toxicity test was conducted. LC50were calculated using mean analyzed exposure concentrations in a range of 0.25 to 2.67 mg/l. These data were used to determine the maximum acceptable toxicant concentration (MATC), that is defined as the theoretical toxic threshold concentration that falls between the highest concentration showing no effect (NOEC) and the next higher concentration showing a toxic effect (LOEC) when compared to the controls. For survival (immobility, mortality) NOEC and LOEC were not statistically determined but were estimated by observation. (14)

Species: Daphnia magna (Crustacea)
Endpoint: other: growth
Exposure period: 21 day
Unit: mg/l **Analytical monitoring**: yes
NOEC: = 1.78
LOEC: = 2.67
EC50: > 2.67
—–:
Method: OECD Guide–line 202, part 2 "Daphnia sp., Reproduction Test"
Year: 1984

Test substance: as prescribed by 1.1 – 1.4 **GLP:** yes
Result: For growth (length in mm) MATC was determined to be 2.18 mg/l.
Source: Dow Chemical Company
Test condition: A flow–through life–cycle toxicity test was conducted. LC50 were calculated using mean analyzed exposure concentrations in a range of 0.25 to 2.67 mg/l. These data were used to determine the maximum acceptable toxicant concentration (MATC), that is defined as the theoretical toxic threshold concentration that falls between the highest concentration showing no effect (NOEC) and the next higher concentration showing a toxic effect (LOEC) when compared to the controls. (14)

Species: Daphnia magna (Crustacea)
Endpoint: other: immobility
Exposure period: 21 day
Unit: mg/l **Analytical monitoring**: yes
NOEC: = 1.18
LOEC: = 1.78
EC50: = 2.48
–––:
Method: OECD Guide–line 202, part 2 "Daphnia sp., Reproduction Test"
Year: 1984 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Result: For immobility MATC was determined to be 1.45 mg/l.
Source: Dow Chemical Company
Test condition: A flow–through life–cycle toxicity test was conducted. LC50 were calculated using mean analyzed exposure concentrations in a range of 0.25 to 2.67 mg/l. These data were used to determine the maximum a acceptable toxicant concentration (MATC), that is defined as the theoretical toxic threshold concentration that falls between the highest concentration showing no effect (NOEC) and the next higher concentration showing a toxic effect (LOEC) when compared to the controls. For survival (immobility, mortality) NOEC and LOECwere not statistically determined but were estimated by observation. (14)

Species: Daphnia magna (Crustacea)
Endpoint: reproduction rate
Exposure period: 21 day
Unit: mg/l **Analytical monitoring**: yes
NOEC: = 1.18
LOEC: = 1.78
EC50: = 1.1
––– :
Method: OECD Guide–line 202, part 2 "Daphnia sp., Reproduction Test"
Year: 1984 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Result: For reproduction (mean total young/adult) MATC was determined to be 1.45 mg/l.

Source: Dow Chemical Company
Test condition: A flow–through life–cycle toxicity test was conducted. LC50 were calculated using mean analyzed exposure concentrations in a range of 0.25 to 2.67 mg/l. These data were used to determine the maximum acceptable toxicant concentration (MATC), that is defined as the theoretical toxic threshold concentration that falls between the highest concentration showing no effect (NOEC) and the next higher concentration showing a toxic effect (LOEC) when compared to the controls. (14)

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

Type:
Species:

Endpoint:
Exposure period:
Unit:
Method:
Year: **GLP:**
Test substance:
Remark: no data available
Source: Dow Chemical Company

4.6.2 Toxicity to Terrestrial Plants

Species:
Endpoint:
Expos. period:
Unit:
Method:
Year: **GLP:**
Test substance:
Remark: no data available
Source: Dow Chemical Company

4.6.3 Toxicity to other Non–Mamm. Terrestrial Species

Species:
Endpoint:
Expos. period:
Unit:
Method:
Year: **GLP:**
Test substance:
Remark: no data available
Source: Dow Chemical Company

4.7 Biological Effects Monitoring
Remark: no data available
Source: Dow Chemical Company

4.8 Biotransformation and Kinetics
Type:
Remark: no data available
Source: Dow Chemical Company

4.9 Additional Remarks
Remark: no additional remarks
Source: Dow Chemical Company

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 1182 mg/kg bw (females); 1414 mg/kg bw (males)
Method: other: EPA Health Effects Test Guidelines
Year: 1982 **GLP:** yes
Test substance: no data
Remark: Five rats/sex received 500, 1000, or 2000 mg/kg of TCP. Male rats were less susceptible to TCP (1414 mg/kg) than female rats (1182 mg/kg). Clinical observations included lethargy, loss of coordination, palpebral closure, lacrimation and/or labored respiration in some animals of all dose groups. All survivors appeared normal within four days post–treatment and gained weight by study termination. At necropsy, rats that died during the study had several nonspecific observations attributed to terminal change and stress. Rats that survived the observation period were within normal limits. Based on these results, 2,3,5,6–tetrachloropyridine was categorized as low in acute oral toxicity.
Source: Dow Chemical Company (15)

Type: other: Range finding study
Species: rat
Sex: female
Number of Animals: 2
Vehicle: corn oil
Value: = LD50 approximately 1000 mg/kg
Method: other: not specified
Year: **GLP:** no data
Test substance: no data
Remark: TCP was fed (not specified) as a 10% solution in corn oil, by a single dose oral gavage at concentrations of 126, 252, 500, 1000, or 2000 mg/kg body weight (2 female rats at each dose level). No deaths occurred in the 500 mg/kg group, but animals showed slight liver and kidney injuries at autopsy. At 1000 and 2000 mg TCP/kg bw one out of two and both animals died, respectively. Liver and kidney injuries were observed in all animals. In addition, 2000 mg TCP/kg bw produced lung congestion and pneumonia.
Source: Dow Chemical Company (16), (17)

5.1.2 Acute Inhalation Toxicity

Type: other: Toxicity evaluation
Species: rat
Sex:
Number of Animals:
Vehicle:
Exposure time: 7 hour(s)
Value: = 6300 ppm
Method: other: not specified
Year: **GLP:** no data
Test substance: no data

Remark: Six male Sprague–Dawley (Spartan substrain) rats were exposed (whole–body) to approx. 6300 ppm (56 mg/l) TCP. No signs of toxicity were seen in any of the exposed rats during or after exposure. All exposed rats showed body weight gain comparable to control rats during the two week post–exposure observation period. No treatment–related lesions were seen in any of the rats at necropsy.
Source: Dow Chemical Company (18)

5.1.3 Acute Dermal Toxicity

Type:
Species:
Sex:
Number of Animals:
Vehicle:
Value:
Method:
Year: **GLP:**
Test substance:
Remark: no data available
Source: Dow Chemical Company

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: i.p.
Value: = 1150 mg/kg bw
Method: other: see reference
Year: 1967 **GLP:** no data
Test substance: other TS: purity >97%
Source: Dow Chemical Company (5)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: Neat
Exposure:
Exposure Time: applications over a 14-day period
Number of Animals:
PDII:
Result: not irritating

EC classificat.:
Method: other: not specified
Year: **GLP:** no data
Test substance: no data
Remark: Solid TCP repeatedly (3 to 10 applications) applied to the intact or abraded belly of rabbits had only a very slight effect on the skin (slight hyperemia), that disappeared after a few days.
Source: Dow Chemical Company (16), (17)

Species: rabbit
Concentration: 20% in perchloroethylene
Exposure: 24 hours
Exposure Time: 14-day period
Number of Animals:
PDII:
Result: Material is unlikely to be absorbed in acutely toxic amount at the levels tested.
EC classificat.:
Method: other: not specified
Year: **GLP:** no data
Test substance: no data
Remark: 20%TCP in perchloroethylene repeatedly for 3 or 10 applications applied to the intact & abraded belly or intact ear of rabbits. The ear had a slight effect on the skin (slight hyperemia) after three days and a very slight necrosis appearing at the beginning of the second week and clearing at the end of second week. The intact belly had moderate hyperemia after the second day. Slight necrosis appeared at the beginning of the second week, along with slight edema and moderate exfoliation, clearing at the end of the second week. The abraded belly had slight hyperemia, moderate edema and moderate necrosis at height the end of the first week, almost cleared at the end of second week.
Source: Dow Chemical Company (16), (17)

5.2.2 Eye Irritation

Species: rabbit
Concentration: neat
Dose:
Exposure Time: one eye-30 seconds then washed with water; one hour and then washed
Comment:
Number of Animals: one
Result: not irritating
EC Classificat:
Method: other: not specified
Year: **GLP:** no data
Test substance: no data
Remark: Undiluted TCP administered to the eyes of rabbits (washed or unwashed after application) caused very slight pain and very slight prominence of conjunctival capillaries. An almost complete clearing was observed within one hour.
Source: Dow Chemical Company (16), (17)

5.3 Sensitization

Type: no data

Species: guinea pig
Number of Animals: five/sex
Vehicle: Dipropylene glycol monomethyl ether:Tween 80 mixture
Result: not sensitizing
Classification:
Method: other: according to Maguire
Year: **GLP:** no data
Test substance: as prescribed by 1.1 – 1.4
Remark: Five male and five female Hartley guinea pigs received six topical 0.5 ml applications of the test material, which had been diluted in a 9:1 DPGME*:Tween 80 mixture, during a two–week induction phase. TCP was applied as a 5% solution to the clipped portion of the abdomen. After a two–week rest period, the guinea pigs were challenged with 0.3 ml of TCP or vehicle. The application sites were evaluated after 24 and at 48 hours for evidence of erythema and/or edema. None of the animals had erythema or edema due to the test solution or the vehicle. Therefore, under the conditions of this study, TCP did not cause delayed contact hypersensitivity in guinea pigs. (*=Dipropylene glycol monomethyl ether)
Source: Dow Chemical Company (19), (17)

5.4 Repeated Dose Toxicity

Species: rat Sex: male/female
Strain: Sherman
Route of admin.: oral feed
Exposure period: 91 days
Frequency of treatment: daily diet ad libitum
Post. obs. period: no
Doses: 1, 3, 10, 30, 100 mg/kg/day
Control Group: yes, concurrent vehicle
NOAEL: = 100 mg/kg bw
LOAEL: =
Method: other: see remark
Year: **GLP:** no
Test substance: as prescribed by 1.1 – 1.4
Remark: Groups of 10 rats/sex were used. Parameters evaluated included clinical observations, body weights, feed consumption, hematology, clinical chemistry, organ weights, and gross and histopathologic alterations.

Result: The male rats receiving 100 or 30 mg/kg/day of the test material had increased kidney weights, and on gross examination the kidneys from these groups were pale in color. Histopathologic examination revealed mild, reversible degenerative changes (hyaline droplet) in the kidneys from males at the 100, 30 and 10 mg/kg/day dosage levels. Since these changes are male specific and considered to be reversible, the toxicological significance had little relevance to humans. The average liver weight of the males at 100 mg/kg/day had slightly increased, but no compound–related changes were observed microscopically. No evidence of compound–related effects was observed in male rats receiving 3 or 1 mg/kg/day of the test material.
The female rats did not show the kidney changes in color, weight or histopathology at any dosage level. Although females at 100 and 30 mg/kg/day had slightly increased liver and spleen weights, no compound–related changes were apparent microscopically in these organs. Hence, the weight increases were not considered toxicologically significant in the view of the lack of histopathologic changes in these

organs. No evidence of compound– related effects was observed in female rats at 10 mg/kg/day or below.
Source: Dow Chemical Company (20)

Species: rat **Sex**: male/female
Strain: Sprague–Dawley
Route of admin.: gavage
Exposure period: approx. 52 days
Frequency of treatment: one dose/day
Post. obs. period: no
Doses: 5, 25, 150 mg/kg/day
Control Group: yes, concurrent vehicle
NOAEL: = 25 mg/kg bw (females); 150 mg/kg bw (males)
LOAEL: =
Method: other: see remark
Year: **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Remark: Groups of 15 rats/sex were used. After 2 weeks of dosing, the parental rats were mated for two weeks to produce the F1 litters. Dosing of both sexes continued through the gestation and lactation period. All parental animals and litters were euthanatized following lactation day 4. Parental parameters evaluated included clinical observations, body weights, feed consumption, hematology, clinical chemistry, organ weights, and gross and histopathology, and fertility. Neonatal parameters evaluated included clinical/morphological alterations, body weight and survival.

Result: No significant treatment–related effects were observed on clinical alterations, feed consumption, body weight or body weight gain at any dose level. Parental males and females given 150 mg/kg/day had pale kidneys, increased liver and kidney weights, centrilobular hypertrophy of hepatocytes, and histologic alterations in kidneys. The renal effects included protein droplet nephropathy in males and slight to severe tubule epithelial cell degeneration/regeneration, very slight to slight distension of tubules, and inflammation of papilla(e) in females. Protein droplet nephropathy was also observed in males given 2 mg/kg/day. The liver changes in males and females were consistent with compensatory increases in metabolic activity and was not considered toxicologically significant. The protein droplet nephropathy in males was not considered relevant to human risk assessment as this effect is a male rat specific response. Alterations in a number of clinical chemistry parameters were also observed in females given 150mg/kg/day and were considered secondary to renal and hepatic effects. All other statistically significant changes in the parameters of parental rats given TCP were not considered toxicologically s significant as the altered parameters were within normal values or were not supported by histologic changes in corresponding tissues.
Source: Dow Chemical Company (21)

5.5 Genetic Toxicity ’in Vitro’

Type: Ames test
System of testing: Salmonella typhimurium baterial tester strains TA98, TA100, TA1335, TA1537
Concentration: 5 though 5000 µg/plate (bacteria toxicity); 0.5 through 166.7 µg/plate (genotoxicity)
Metabolic activation: with and without
Result: negative

Method: OECD Guide–line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
Year: 1983 **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Remark: Test was conducted using a pre–incubation modification of the standard assay (Ames test) and in presence and absence of an externally supplied metabolic activation system. Two independent assays were conducted in each tester strain. The concentrations of the test material ranged from 5 through 5000 µg/plate in the range finding assay with TA100. Toxicity to bacteria was noted in doses without activation starting at 50 µg/plate and with activation at 166.7µg/plate. In the mutagenicity assay with all four tester strains the doses used were 0.5 through 50µg/plate without activation and 1.67 through 166.7 µg/plate with activation. The test material did not induce a mutagenic response in any of the tester strains as judged by the frequency of histidine–independent (his+) revertants. The test material was classified as negative in the Ames test under the experimental conditions used.
Source: Dow Chemical Company (13)

5.6 Genetic Toxicity ’in Vivo’

Type: Micronucleus assay
Species: mouse **Sex:** male/female
Strain: CD–1
Route of admin.: gavage
Exposure period: single injection
Doses: 22.5; 75; 225 mg/kg (male) and 93; 310; 930 mg/kg (female)
Result:
Method: other: in line with OECD (1981), EEC (1984) and U.S. EPA (1985) guidelines
Year: **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Remark: Type of cell used were mouse bone marrow micronucleus, erythrocytes. The test is capable of detecting agents causing chromosomal aberrations and spindle malfunction. The dose levels were based on the outcome of a range finding assay. Mice treated with cyclophosphamide (120 mg/kg) were used as positive control group and sacrificed 24 post treatment. TCP–treated animals were sacrificed 24, 48, or 72 hours after treatment. One thousand polychromatic erythrocytes (PCE) were evaluated from each surviving animal and the frequencies of micronucleated polychromatic erythrocytes (MN–PCE) were recorded.

Result: There were no significant increases in the frequencies of MN–PCE in groups treated with the test material as compared to negative controls. The positive control mice showed significant increases in MN–PCE. Under the experimental conditions used, the test material was considered to be negative in the mouse bone marrow micronucleus test.
Source: Dow Chemical Company (22)

5.7 Carcinogenicity

Species: **Sex:**
Strain:
Route of admin.:
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Result:

Control Group:
Method:
Year: **GLP:**
Test substance:
Remark: no data available
Source: Dow Chemical Company

5.8 Toxicity to Reproduction

Type: other: reproductive/developmental toxicity screen
Species: rat **Sex:** male/female
Strain: Sprague–Dawley
Route of admin.: gavage
Exposure Period: approx. 52 days
Frequency of treatment: one dose/day
Premating Exposure Period
male: 14 days
female: 14 days
Duration of test: approx. 52 days
Doses: 5, 25, 150 mg/kg/day
Control Group: yes, concurrent vehicle
NOEL: = 150 mg/kg/day for reproductive and developmental toxicity
NOAEL Parental: = 25(females); 150 (males) mg/kg bw
NOAEL F1 Offspr.: = 150 mg/kg bw
NOAEL F2 Offspr. : =
Method: other: see remark
Year: **GLP:** yes
Test substance: as prescribed by 1.1 – 1.4
Remark: Groups of 15 rats/sex were used. After 2 weeks of dosing, the parental rats were mated for two weeks to produce the F1 litters. Dosing of both sexes continued through the gestation and lactation period. All parental animals and litters were euthanatized following lactation day 4. Parental parameters evaluated included clinical observations, body weights, feed consumption, hematology, clinical chemistry, organ weights, and gross and histopathology, and fertility. Neonatal parameters evaluated included clinical/morphological alterations, body weight and survival.

Result: **N**o significant treatment–related effects were observed on clinical alterations, feed consumption, body weight or body weight gain at any dose level. Parental females given 150mg/kg/day had slight to severe renal tubular epithelial cell degeneration/regeneration, and inflammation of the renal papilla (e). Males given 25 or 150mg/kg/day had protein droplet nephropathy which was not considered relevant to human risk assessment, as this effect is a male rat–specific response. Increased liver weights and centrilobular hypertrophy of hepatocytes occurred in males and females given 150 mg/kg/day. Liver weight and histologic differences were interpreted to be an adaptive change, secondary to the metabolism of TCP, and were not considered toxicologically significant. Alterations in a number of clinical chemistry parameters were also observed in females given 150 mg/kg/day and were considered secondary to renal and hepatic effects. No effects attributed to treatment were observed on pregnancy rate, time to mating, gestation length, number of corpora lutea or implantations, preimplantation or postimplantation loss, fertility indices, litter size, neonatal growth or survival, or testes and epididymides weights at any dose level. In addition, no gross or histopathologic alterations of the testes, epididymides or ovaries were observed at 150 mg/kg/day.
Source: Dow Chemical Company (21)

5.9 Developmental Toxicity/Teratogenicity

Species: **Sex:**
Strain:
Route of admin.:
Exposure period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:**
Test substance:
Remark: no data available
Source: Dow Chemical Company

5.10 Other Relevant Information

Type: Pharmacokinetic fate
Remark: Male and female Fischer 344 rats were administered a single dose of either 1 or 1000 mg TCP/kg by intraperitoneal injection with blood and urinary concentrations of TCP determined by gas chromatography.
Source: Dow Chemical Company (23)

5.11 Experience with Human Exposure

Remark: No data of human exposure to 2,3,5,6–TCP are available.
Source: Dow Chemical Company

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(15) Jeffrey et al. (1987) "Tetrachloropyridine: Acute oral toxicity in Fischer 344 rats", unpublished report of The Dow Chemical Company

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(20) McCollister SB and Sparschu GL (1969) "Results of 91–day dietary feeding studies of 2,3,5,6–tetrachloropyridine in rats", unpublished report of The Dow Chemical Company

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7.1 Risk Assessment

–

201-16113

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I U C L I D

Data Set

Existing Chemical	: ID: 17824-83-8
CAS No.	: 17824-83-8

Producer related part

Company	: The Dow Chemical Company
Creation date	: 11.12.2003

Substance related part

Company	: The Dow Chemical Company
Creation date	: 11.12.2003
Status	:
Memo	:
Printing date	: 08.12.2005
Revision date	:
Date of last update	: 08.12.2005
Number of pages	: 16
Chapter (profile)	: Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	: Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	: Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	other: lead company
Name	:	The Dow Chemical Company
Contact person	:	
Date	:	
Street	:	2020 Dow Center
Town	:	48674 Midland, Michigan
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

11.12.2003

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	
Substance type	:	organic
Physical status	:	solid
Purity	:	
Colour	:	
Odour	:	
Reliability	:	(1) valid without restriction

11.12.2003

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

3,4,5,6-tetrachloro-2-pyridine carbonitrile

11.12.2003

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= 150.5 - 151.5 °C
Sublimation	:	
Method	:	other
Year	:	1977
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	GLP not compulsory at time study was performed.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

27.09.2004 (1)

2.2 BOILING POINT

Value	:	= 310.1 °C at
Decomposition	:	
Method	:	other: calculated
Year	:	2003
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Value calculated using EPA's programs.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

27.09.2004 (2)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= .000044475 hPa at 25 °C
Decomposition	:	
Method	:	other (calculated)
Year	:	2003
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Value calculated using EPA's programs.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

27.09.2004 (2)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	= 2.93 at 25 °C
pH value	:	

Method	:	other (calculated)
Year	:	2003
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Value calculated using EPA's programs.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

27.09.2004 (3)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	= 45 mg/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	other: calculated
Year	:	2003
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Value calculated using EPA's programs.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

08.12.2005 (4)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

Result	:	no oxidizing properties
Method	:	other: estimated
Year	:	2003
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Remark	:	Not Applicable. Not expected to have significant oxidizing or reducing

potential.

Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
27.09.2004

2.12 DISSOCIATION CONSTANT

Method : other: calculated
Year : 2003
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Not applicable. Does not ionize within environmentally relevant pH ranges.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
27.09.2004

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

INDIRECT PHOTOLYSIS

Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	= .0000000000028 cm^3/(molecule*sec)
Degradation	:	= 50 % after 3881 day(s)
Deg. product	:	
Method	:	other (calculated)
Year	:	2004
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Values are calculated using the EPA's programs.
Result	:	The rate constant for the vapor phase reaction with photochemically produced hydroxyl radicals is estimated to be 0.0028E-12 cm3/molecule-sec at 25C; which corresponds to a tropospheric half-life of 3880.975 days, (12-hr day; 1.5E+06 OH/cm3).
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

31.08.2005 (5)

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	
Air	:	1.5 % (Fugacity Model Level I)
Water	:	55.6 % (Fugacity Model Level I)
Soil	:	41.9 % (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	82.2 % (Fugacity Model Level II/III)
Method	:	other
Year	:	2005
Remark	:	Values calculated using EPA's programs.
Source	:	The Dow Chemical Company, Midland, MI.
Attached document	:	carbonitrileFugacity.doc
Reliability	:	(2) valid with restrictions

08.12.2005 (6)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Deg. product	:	
Method	:	other: calculated
Year	:	2004
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Values are calculated using EPA's programs.
Result	:	Material is estimated not to biodegrade fast using a linear and non-linear SAR method, and not to be readily biodegradable using a MITI linear and non-linear SAR method. Ultimate and primary biodegradation is estimated to occur in weeks-months and days-weeks, respectively.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

27.09.2004 (7)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

BCF	:	= 35.95
Elimination	:	
Method	:	other: calculated
Year	:	2004
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Value calculated using EPA's programs.
Source	:	The Dow Chemical Company, Midland, MI.
Reliability	:	(1) valid without restriction

27.09.2004 (8)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : other: calculated
Species : other: fish
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 25.956 calculated
Method : other: calculated
Year : 2004
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Value calculated using EPA's programs.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
27.09.2004 (9)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : other: calculated
Species : other: Daphnid
Exposure period : 48 hour(s)
Unit : mg/l
EC50 : = 27.373 calculated
Method : other: calculated
Year : 2004
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Value calculated using EPA's programs.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
27.09.2004 (9)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species :
Endpoint :
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : = 18.054 calculated
Method : other: calculated
Year : 2004
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Value calculated for green algae using EPA's programs.
Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
27.09.2004 (9)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 1000 - 2000 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	female
Number of animals	:	10
Vehicle	:	other: corn oil
Doses	:	
Method	:	other
Year	:	1966
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Groups of two female rats/dose level were administered the test material as a 20% suspension in corn oil at dose levels of 252, 500, 1000, 2000, or 3980 mg/kg bw via single-dose oral gavage. The animals were observed frequently on the day of dosing and at least daily thereafter for signs of toxicity for a duration of two weeks. The animals were weighed on the day of dosing, one day post-dosing, and weekly thereafter. At the end of the two-week observation period, animals were submitted to necropsy, and pathological examination was conducted on representative animals.

Result : Both rats given 3980 mg/kg and one rat given 2000 mg/kg died prior to study termination, within a week of treatment. These rats were observed with liver and kidney congestion at necropsy. One rat also had lung pneumonia. All rats given 1000 mg/kg or more had diarrhea and diuresis which resolved within a week. There was no indication that the material causes cyanide-like effects. All rats surviving to study termination appeared normal at necropsy.

Source : The Dow Chemical Company, Midland, MI

Reliability : (2) valid with restrictions
Study was conducted prior to the advent of GLP, but is scientifically sound.

11.12.2003 (10)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other
Value	:	
Species	:	human
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	
Year	:	1967
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Remark : There were 66 reported exposures involving 58 men reported over a 2 month period. Exposure to vapor from heated material resulted in mild respiratory irritation.

Source : The Dow Chemical Company, Midland, MI
11.12.2003 (11)

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species : rabbit
Concentration : undiluted
Exposure : Occlusive
Exposure time : 24 hour(s)
Number of animals : 2
Vehicle :
PDII :
Result : corrosive
Classification :
Method : other
Year : 1966
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : White laboratory rabbits were shaved on the abdomen using a straight razor and barber soap. Animals were then rested for several days to allow any abrasions to heal completely and to be sure skin was suitable for use. Aliqots of the test material were applied to both intact and abraded sites on the abdomen under cotton pads and cloth bandages. Application was repeated for up to 10 days or until a substantial burn occurred. In addition, another rabbit was treated in a similar fashion with a 10% solution of the test material in dipropylene glycol monomethyl ether.
Result : Rabbits were treated with two consecutive applications of the undiluted test material before a moderate burn occurred. Applications were then discontinued, but animals were observed for another 8 days. Burn sites appeared to heal normally within that period. The rabbit treated with a 10% solution of the test material died overnight, likely due to enhanced absorption of the material.
Source : The Dow Chemical Company, Midland, MI
Reliability : (2) valid with restrictions
Study was conducted prior to the advent of GLP, but is considered scientifically sound.
11.12.2003 (10)

Species : human
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
PDII :
Result :
Classification :
Method :
Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : There were 66 reported exposures involving 58 men reported over a 2 month period. Signs and symptoms from skin exposure were delayed 2-24 hours unless the material was hot. Effects ranged from redness and a burning sensation to moderate burns which appeared to be exacerbated by clothing friction, chemical confinement, and sweating.
Source : The Dow Chemical Company, Midland, MI
11.12.2003 (11)

5.2.2 EYE IRRITATION

Species : rabbit
Concentration : undiluted
Dose : .1 other: mg
Exposure time : 1 hour(s)
Comment :
Number of animals : 1
Vehicle :
Result : moderately irritating
Classification :
Method : other
Year : 1966
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Aliquots of the undiluted test material were instilled into both eyes of white rabbit. One eye was left unwashed, while the other eye was rinsed under running water within 1 hour of instillation. The rabbit was observed for 7 days for signs of conjuntival or iridial irritation as well as corneal injury, both with and without fluoroscein stain. The test was terminated after 7 days.
Result : Instillation of the test material produced slight to moderate conjunctival redness, with no evidence of corneal or iridial effects. The irritation resolved within 7 days.
Source : The Dow Chemical Company, Midland, MI
Reliability : (2) valid with restrictions
Study was conducted prior to the advent of GLP, but is considered scientifically sound.
11.12.2003 (11)

Species : human
Concentration :
Dose :
Exposure time :
Comment :
Number of animals :
Vehicle :
Result :
Classification :
Method :
Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : There were 66 reported exposures involving 58 men reported over a 2 month period. Eye exposure to vapors resulted in slight to moderate conjunctival irritation and slight to severe corneal injury.
Source : The Dow Chemical Company, Midland, MI
19.09.2005 (11)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

5.5 GENETIC TOXICITY ‘IN VITRO‘

5.6 GENETIC TOXICITY ‘IN VIVO‘

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

Type : other: TOPKAT and DEREK QSAR Analysis

Attached document : 3 4 5 6-Tetrachloro-2-pyridine carbonitrile.doc
Chlorinated Pyridines.xls

08.12.2005

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

9. References

(1) Ruetman, S.H.; Synthesis 1977 (10) P716

(2) MPBPWIN v1.41, © 2000 U.S. EPA

(3) KOWWIN v1.67, © 2000 U.S. EPA

(4) WSKOWWIN v1.41, © 2004 U.S. EPA

(5) U.S. EPA, 2000. - AOPWin, v1.91, Atmospheric half-life estimating software & experimental value database.

(6) U.S. EPA, 2003. - EPIWin, v3.12; WVOLNT.exe volatilization half-life est. software; & EPI_PHYS.db phys. property database.

(7) U.S. EPA, 2000. - BIOWin, v4.01, Biodegradation probability estimating software.

(8) EPA, 2000. - BCFWin, v2.15, Bioconcentration factor (BCF) estimating software.

(9) Cash, G. & V. Nabholz., 2001. U.S. EPA OPPT - ECOSAR, v0.99g, Aquatic organism toxicity estimating software.

(10) Unpublished data, The Dow Chemical Company.

(11) Unpublished data, The Dow Chemical Company

10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

Chapter : Toxicity
Memo : Comparison of DEREK results for test material and pentachloropyridine

Remark :

DEREK for Windows report

Date Created: Monday, December 08, 2003
Version: 7.0.0
Database: N:\Private\Lhasa Ltd\LPS 700\Dfw700.mdb
Database Version: DFW7.0.0_22_09_2003
Testing Against: All Alerts

Species: bacterium
mammal
Salmonella typhimurium
SuperEndpoints: Carcinogenicity
Genotoxicity
Irritation
Miscellaneous endpoints
Respiratory sensitisation
Skin sensitisation
Thyroid toxicity
Consider Tautomers: True
Hydrogen Options: Perceive implicit and explicit hydrogens
Override automatic Log P calculation: False
AutoSave: Off
AutoSave Directory: N:\Private\Lhasa Ltd\LPS 700\work
Name Field:

Compound Name: Tetrachloro-2-cyanopyridine picolinonitrile

Log Kp: -2.666 Calculated by the Potts & Guy equation
Log P: 2.154 Calculated by the Moriguchi estimation
Molecular Weight: 241.892 Calculated by LPS

Submitted Compound:

List of alerts found:

438 Activated pyridine, quinoline or isoquinoline. Skin sensitisation.
Number of matches = 2

LHASA PREDICTIONS

Skin sensitisation

mammal - Reasoning

Skin sensitisation in mammal is PLAUSIBLE
[Skin sensitisation alert] is [CERTAIN]
[species mammal] is [CERTAIN]

Alert overview: 438 Activated pyridine, quinoline or isoquinoline

Electrophilic substituted pyridines, quinolines or isoquinolines may react with skin protein via a SnAr mechanism. Nucleophilic substitutions proceed slowly at aromatic carbons, but compounds of this type are susceptible to nucleophilic attack at the ring carbon attached to R1 in the presence of electron withdrawing groups in the ortho and para ring positions. The ring nitrogens can exert a strong activation, and may behave analogously to nitro groups on activated benzenes (alert 415). The activation is enhanced further if the ring nitrogen is positively charged as N-oxide or N-Me. The reactivity of these compounds is dependent on the combination of the strength of the leaving group R1, and the strength and number of the electron withdrawing groups R2 [Roberts, March, Landsteiner and Jacobs, De Boer and Dirkx].

The presence of a skin sensitisation structural alert within a molecule indicates the molecule has the potential to cause skin sensitisation. Whether or not the molecule will be a skin sensitiser will also depend upon its percutaneous absorption. Generally, small lipophilic molecules are more readily absorbed into the skin and are therefore more likely to cause sensitisation.

References:

Title: Studies on the sensitization of animals with simple chemical compounds. II.
Author: Landsteiner K and Jacobs J.
Source: Journal of Experimental Medicine, 1936, 64, 625-639.

Title: Annex to commission directive 93/72/EEC of 1 September 1993 adapting to technical progress for the nineteenth time council directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, ...
Author: Commission of the European Communities.
Source: Official Journal of the European Communities, 1993, 36 (L258A), 1-1409.

Title: Linear free energy relationships for reactions of electrophilic halo- and pseudohalobenzenes, and their application in prediction of skin sensitization potential for SnAr electrophiles.
Author: Roberts DW.
Source: Chemical Research in Toxicology, 1995, 8, 545-551.

Title: Aromatic nucleophilic substitution.
Author: March J.
Source: Advanced organic chemistry. Reactions, mechanisms, and structure, 3rd edition, March J, Wiley-Interscience, New York, 1985, 576-607.

Title: Activating effects of the nitro group in aromatic substitutions.
Author: De Boer TJ and Dirkx IP.
Source: The Chemistry of the nitro and nitroso groups. Part 1,

Chapter 8, Feuer H (editor), Interscience Publishers, New York, 1969, 487-612.

Locations:

Examples: (438 Activated pyridine, quinoline or isoquinoline)

Example 1. 2-fluoro-5-trifluoromethylpyridine
CAS Number: 69045-82-5

Test Data: (2-fluoro-5-trifluoromethylpyridine)

1.
Species: unspecified
Assay: unspecified
Result: R43

References:

Title: Annex to commission directive 93/72/EEC of 1 September 1993 adapting to technical progress for the nineteenth time council directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, ...
Author: Commission of the European Communities.
Source: Official Journal of the European Communities, 1993, 36 (L258A), 1-1409.

Example 2. 2,3,5,6-tetrachloro-4-(methylsulphonyl)pyridine
CAS Number: 13108-52-6

Test Data: (2,3,5,6-tetrachloro-4-(methylsulphonyl)pyridine)

1.
Species: unspecified
Assay: unspecified
Result: R43

References:

Title: Commission directive 94/69/EC of 19 December 1994 adapting to technical progress for the twenty-first time council directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging ...
Author: Commission of the European Communities.
Source: Official Journal of the European Communities, 1994, 37 (L381), 1-1485.

DEREK for Windows report

Date Created: Monday, December 08, 2003

Version: 7.0.0
Database: N:\Private\Lhasa Ltd\LPS 700\Dfw700.mdb
Database Version: DFW7.0.0_22_09_2003
Testing Against: All Alerts

Species: bacterium
mammal
Salmonella typhimurium
SuperEndpoints: Carcinogenicity
Genotoxicity
Irritation
Miscellaneous endpoints
Respiratory sensitisation
Skin sensitisation
Thyroid toxicity
Consider Tautomers: True
Hydrogen Options: Perceive implicit and explicit hydrogens
Override automatic Log P calculation: False
AutoSave: Off
AutoSave Directory: N:\Private\Lhasa Ltd\LPS 700\work
Name Field:

Compound Name: 2,3,4,5,6-pentachloropyridine

Log Kp: -2.45 Calculated by the Potts & Guy equation
Log P: 2.54 Calculated by the Moriguchi estimation
Molecular Weight: 251.327 Calculated by LPS

Submitted Compound:

List of alerts found:

438 Activated pyridine, quinoline or isoquinoline. Skin sensitisation.
Number of matches = 3

LHASA PREDICTIONS

Skin sensitisation

mammal - Reasoning

Skin sensitisation in mammal is PLAUSIBLE
[Skin sensitisation alert] is [CERTAIN]
[species mammal] is [CERTAIN]

Alert overview: 438 Activated pyridine, quinoline or isoquinoline

Electrophilic substituted pyridines, quinolines or isoquinolines may react with skin protein via a SnAr mechanism. Nucleophilic substitutions proceed slowly at aromatic carbons, but compounds of this type are susceptible to nucleophilic attack at the ring carbon attached to R1 in the presence of electron withdrawing groups in the ortho and para ring positions. The ring nitrogens can exert a strong activation, and may behave analogously to nitro groups on activated benzenes (alert 415). The activation is enhanced further if the ring nitrogen is positively charged as N-oxide or N-Me. The reactivity of these compounds is dependent on the combination of the strength of the leaving group R1, and the strength and number of the electron withdrawing groups R2 [Roberts, March, Landsteiner and Jacobs, De Boer and Dirkx].

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Title: Aromatic nucleophilic substitution.
Author: March J.
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Title: Activating effects of the nitro group in aromatic substitutions.
Author: De Boer TJ and Dirkx IP.
Source: The Chemistry of the nitro and nitroso groups. Part 1, Chapter 8, Feuer H (editor), Interscience Publishers, New York, 1969, 487-612.

Locations:

Examples: (438 Activated pyridine, quinoline or isoquinoline)

Example 1. 2-fluoro-5-trifluoromethylpyridine
CAS Number: 69045-82-5

Test Data: (2-fluoro-5-trifluoromethylpyridine)

1.
Species: unspecified
Assay: unspecified
Result: R43

References:

Title: Annex to commission directive 93/72/EEC of 1 September 1993 adapting to technical progress for the nineteenth time council directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, ...
Author: Commission of the European Communities.
Source: Official Journal of the European Communities, 1993, 36 (L258A), 1-1409.

Example 2. 2,3,5,6-tetrachloro-4-(methylsulphonyl)pyridine
CAS Number: 13108-52-6

Test Data: (2,3,5,6-tetrachloro-4-(methylsulphonyl)pyridine)

1.
Species: unspecified
Assay: unspecified
Result: R43

References:

Title: Commission directive 94/69/EC of 19 December 1994 adapting to technical progress for the twenty-first time council directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging ...
Author: Commission of the European Communities.
Source: Official Journal of the European Communities, 1994, 37 (L381), 1-1485.

Source : The Dow Chemical Company, Midland, MI.
Reliability : (1) valid without restriction
27.09.2004

10.3 RISK ASSESSMENT